Diastereoselective Spiroannulation of Phenolic Derivatives: Effect of Steric Hindrance on the Diastereoselectivity

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Abstract

The objective of this study was to determine the effect, if any, that steric factors have on the oxidative spiroannulation of simple phenols bearing substituents that are increasing in size. Specifically, we wanted to determine whether or not the diastereoselectivity of the reaction would improve. To do so, the synthesis of five phenols was carried out; from which four of the five spiroether targets were synthesized. Based on the ^{1}H-NMR of these four compounds, it was found that the diastereoselectivity in these reactions did not improve; it actually decreased. The fact that the diastereomeric ratios did not improve with increasing steric factors provides evidence that the spiroannulation is not affected by the size of the group attached to the 3-position. Instead, it gives supporting evidence that the stereoelectronic effect and location of the substituent has greater effect to the overall outcome of the reaction.

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Chapter 1

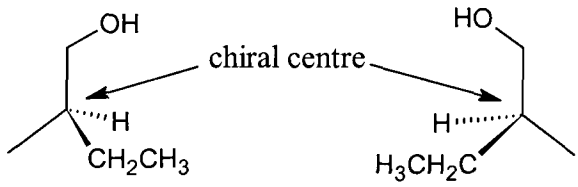
Introduction

1.1 General

Due to the overuse of antibiotics, many strains of bacteria are becoming antibiotic resistant. These resistant strains are of great concern to the general public as the complications due to an untreatable infection are high.[1] Many secondary metabolites isolated from organisms are screened for antibiotic activity in hopes that one or more may have the potential to break down a bacteria's resistance. For example, the pitch preparations of *Picea glauca* (white spruce) and *Pinus contorta* (lodgepole pine) used in traditional Carrier medicine were found to show antimicrobial activity against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans* and *Aspergillus fumigates.*[2] These pitches contain active terpenoids, many of which have known antibiotic properties.[2] Of course, these secondary metabolites are usually isolated in small quantities, often at the expense of the natural source. Therefore, synthesizing novel antibiotics which could be effective against these resistant strains without depleting the natural source is of great importance. However, an organism's enzymes are far more effective and efficient than any synthesis known to man and the enzyme is able to impart a particular orientation or handedness to the structure which is often what makes the structure active. Without this handedness, known as chirality, the compound can be ineffective or even have devastating effects.

1.2 Molecular Chirality

One way that chirality can exist is when the molecule possesses a carbon center, known as a stereogenic or chiral centre, which is bonded to four different substituents.[3] An enantiomer is a chiral molecule that has a non-superimposable mirror image; therefore the configurations at all of the chiral centres in the molecule are opposite. An example of a simple chiral molecule is 2-methyl-1-butanol as shown in **Figure 1** with its two enantiomers:



(R)-2-methyl-1-butanol (S)-2-methyl-1-butanol

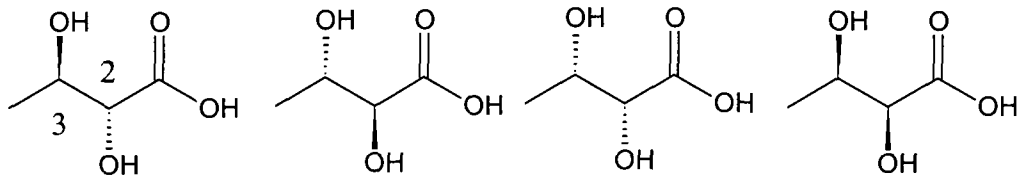
Figure 1: 2-methyl-1-butanol, a simple chiral molecule

The R, S system of nomenclature of enantiomers indicates the configuration of the chiral centre.[4] Pairs of enantiomers have identical physical and chemical properties and as such are difficult to separate or resolve. They are identified by the direction they rotate the plane of polarized light. If a pure enantiomer rotates the plane of polarized light to the right (clockwise direction) it is called dextrorotatory and is indicated by (+) sign. If the light is rotated to the left (counterclockwise direction), it is called levorotatory and is indicated by (-) sign. The specific rotation of the (R)-2-methyl-1-butanol is +5.75° and (S)-2- methyl-1-butanol is -5.75°.[4]

Enantiomerically selective synthesis techniques provide a means of synthesizing one enantiomer over the other.[5] Amongst available techniques, two of high importance include (1) the use of an enzyme to catalyze synthetic transformations and (2) the use of a chiral auxillary. A chiral auxillary is defined as an enantiomerically pure compound that when

attached to a reactant, causes the product with the desired configuration to be formed preferentially. When the reaction is over, the chiral auxillary is removed. Another technique known as chiral pool synthesis uses an enantiomerically pure starting material that has a chiral centre with the needed configuration such as naturally occurring amino acids and carbohydrates.

Compounds that contain more than one chiral centre can form, in theory, a maximum of 2^n stereoisomers where n equals the number of chiral centres. For example, if the molecule contains 1 chiral centre there can exist only 2^1 stereoisomers, in other words, the 2 enantiomers. Diastereomers are configurational isomers that are not enantiomers, meaning they are not mirror images of each other. Diastereomers have different chemical and physical properties. **Figure 2** shows the stereoisomers of 2,3-dihydroxybutanoic acid. The relationship between compounds **1** and **2** is one of enantiomerism, i.e. **1** and **2** are non-superimposable mirror images. Compound **1** has a (2R,3R) configuration while **2** is (2S,3S) or the exact opposite. The same relationship exists between compounds **3** and **4** while **3** has the (2R,3S) configuration and **4** has the opposite, i.e. (2S,3R). Other relationships that exist between these compounds are ones of diastereomerism. For example, **1** (2R,3R) and **3** (2R,3S) are not mirror images since the configuration of C-2 remains the same in both compounds while C-3 changes from R in **1** to S in **3**. Similarly, the relationship of 1/4, 2/3 and 2/4 will be one of diastereomerism. In other words, in order for two stereoisomers to be diastereomers of one another, one of the chiral centres in the molecule must keep its configuration intact while one or more of the other chiral carbons change configurations.

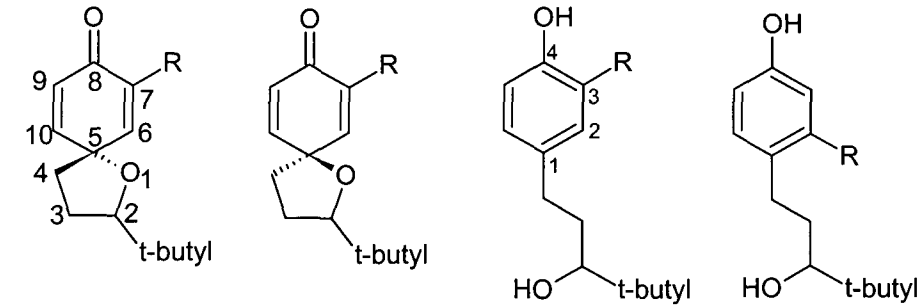


1 **2** **3** **4**

Figure 2: Stereoisomers of 2,3-dihydroxybutanoic acid

1.3 Stereoelectronic vs. steric effects

The type and size of groups attached to a molecule can help determine which diastereomer is predominantly formed over others during a reaction. These are known as stereoelectronic and steric effects respectively. It has been shown that the synthesis of spiroethers, such as **5a** and **5b** (**Figure 3**) where R = OCH_3, from simple phenols can be accomplished diastereoselectively.[6-9] These and other studies[10,11] have shown that the presence of an electron donating group such as R=OCH_3 at the 3 position as shown in structure **6a** not only increases the overall chemical yield of the resulting spiroether but increases the diastereoselectivity as well. This stereoelectronic effect may be the result of the stabilization of a phenoxonium (also known as a phenoxenium) ion **7** (**Figure 4**) by the electron donating group in the transition state.[12,13] This effect has also been observed in the oxidative carbon-based nucleophilic substitution of phenols.[14] Furthermore, it has also been shown that when the R group is located at the 2 position of the aromatic ring (**6b**) instead of the 3 position (**6a**), there is a drastic decrease in the diastereoselectivity (50/50 compared to 81/19) of the reaction as shown in **Scheme 1**.[10,13]



5a (R=OCH_3) **5b** (R=OCH_3) **6a** (R=OCH_3) **6b** (R=OCH_3)

Figure 3: General structures of spiroethers and phenols

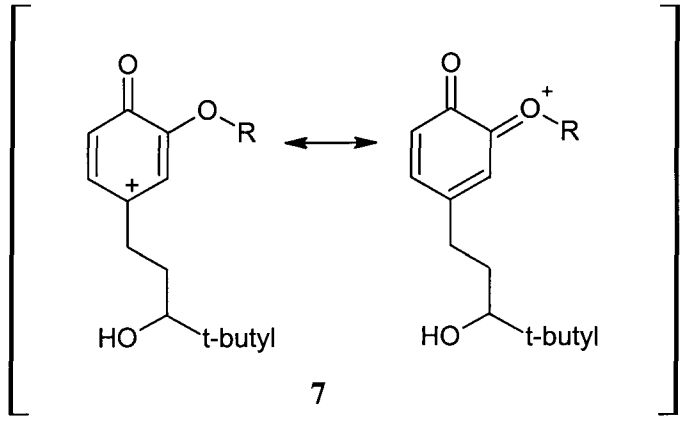
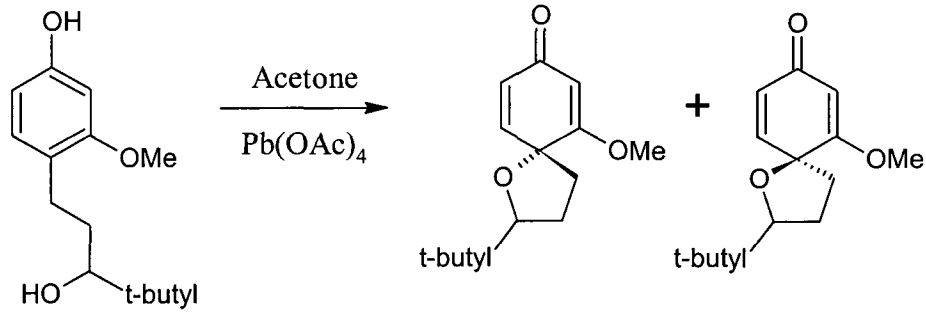


Figure 4: Phenoxonium ion stabilization



Scheme 1: Synthesis of (±)-2-tert-butyl-6-methoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one

A review of the literature suggested that the effect on the diasteroselectivity by large electron donating groups located at the 3 position on **2** has not yet been studied. An investigation of this spiroannulation reaction based on steric effects of the R group would be

a logical complement to the studies of the stereoelectronic effect already published[6,13] and those still ongoing.[10]

1.4 Literature Survey of Spiroannulation Reactions

Normally, spiroannulation reactions tend to form one of four types of cyclohexadienone structures; two with a 2,4-cyclohexadienone backbone and two with a 2,5-cyclohexadienone skeleton as shown in **Figure 5**. Masked ortho benzoquinone ketals (MOB) and o-quinols usually have similar reactivity while masked para benzoquinone ketals (MPB) and p-quinols share an equally similar relationship.[15]

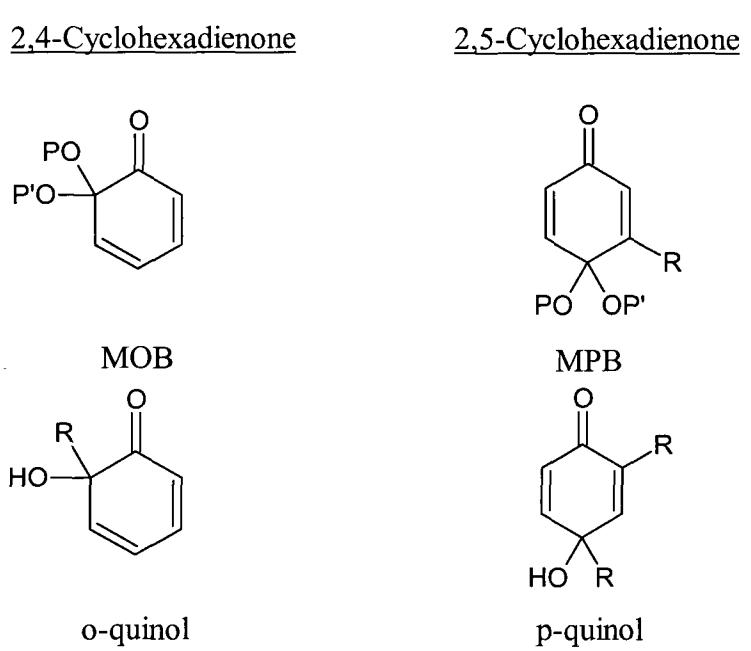
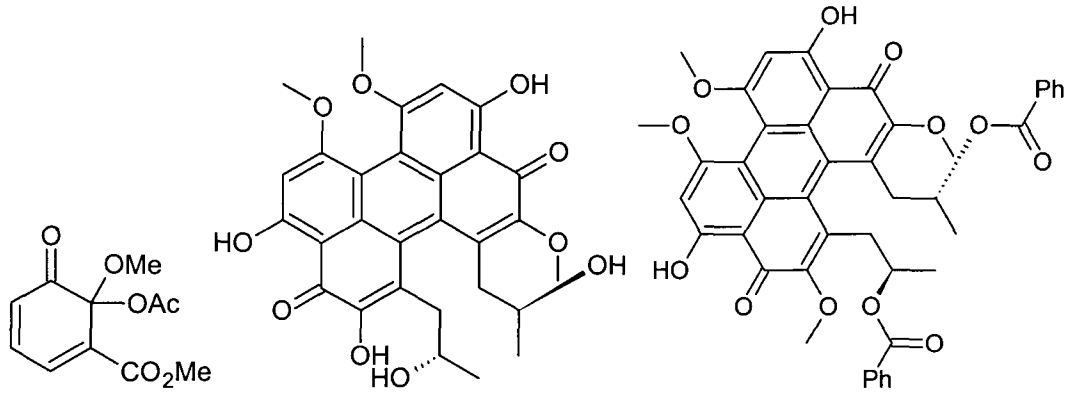


Figure 5: The four types of cyclohexadienone building blocks[15].

These molecules are used as building blocks for the synthesis of many types of natural products. For example, methyl-acetoxy-6-methoxy-1-oxo-2,4-cyclohexadiene-5-carboxylate **8** (**Figure 6**), a 2,4-cyclohexadienone also referred to as an o-quinol acetate, was

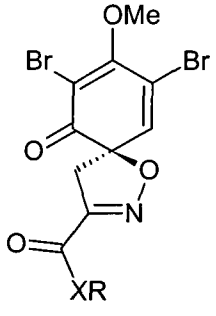
used as a key intermediate in the synthesis of the perylenequinones Phleichrome and Calphostin A.[16] These antibiotics can be isolated from *Cladosporium* species of molds.



8 **Phleichrome** **Calphostin A**

Figure 6: Methyl-acetoxy-6-methoxy-1-oxo-2,4-cyclohexadiene-5-carboxylate

The synthesis of spiroisoxazolines, such as compound **9,** is potentially useful in the parallel synthesis of marine sponge metabolite analogues.[17]

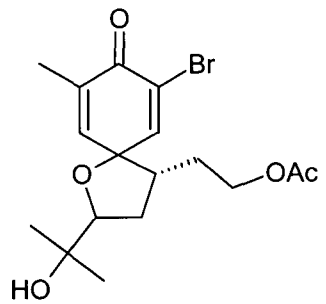


Where XR = OMe or $NHCH_2Ph$

9

Figure 7: An example of a spiroisoxazoline

An example of a 2,5-cyclohexadienone structure used as a building block is the spirodienone **10** which was used in the enantioselective synthesis of heliannuol E, an allelopathogenic substance of sunflowers.[18] Another example is the spirodienone **11** used in the synthesis of Tubersostemonine, a Stemona alkaloid.[19]



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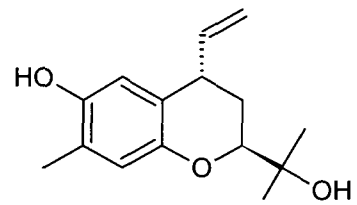
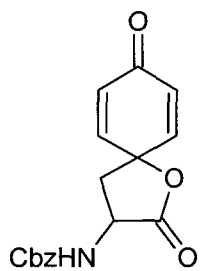


Heliannuol E



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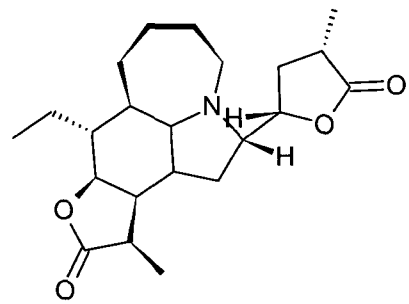
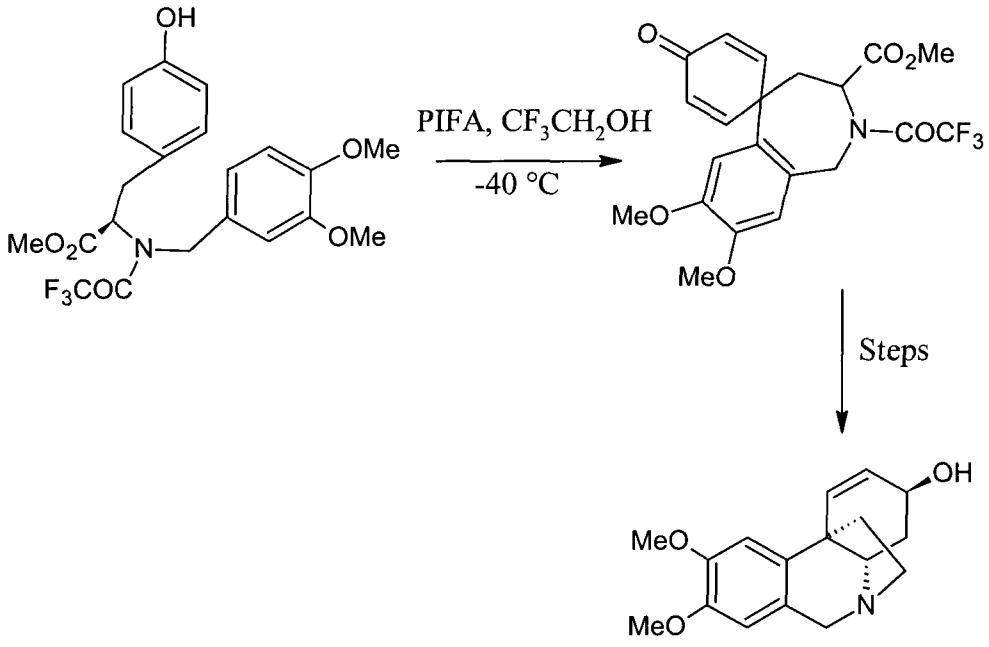


Tubersostemonine

Figure 8: Examples of 2,5-cyclohexadienone structures

The formation of these quinone derivatives is often accomplished by oxidative spiroannulation and oxidative coupling reactions of phenols. Oxidative coupling reactions typically involve the coupling or bringing together of two different R groups, often between two different molecules, which is known as intermolecular coupling. Intramolecular oxidative coupling reactions generating 2,5-cyclohexadienones also exist as demonstrated in **Scheme 2** and **Scheme 3**. Kita and coworkers successfully used an oxidative biaryl coupling reaction of phenol ether derivatives in the total synthesis of a variety of Amaryllidaceae alkaloid derivatives such as (+)-Maritidine (**Scheme 2**).[20-22] Kim and coworkers, investigating the biotransformation of a major drug metabolite in rhesus monkeys, utilized lead tetraacetate in a phenolic oxidation to form compound **12**, also a 2,5-cyclohexadienone core (**Scheme 3**).[23]



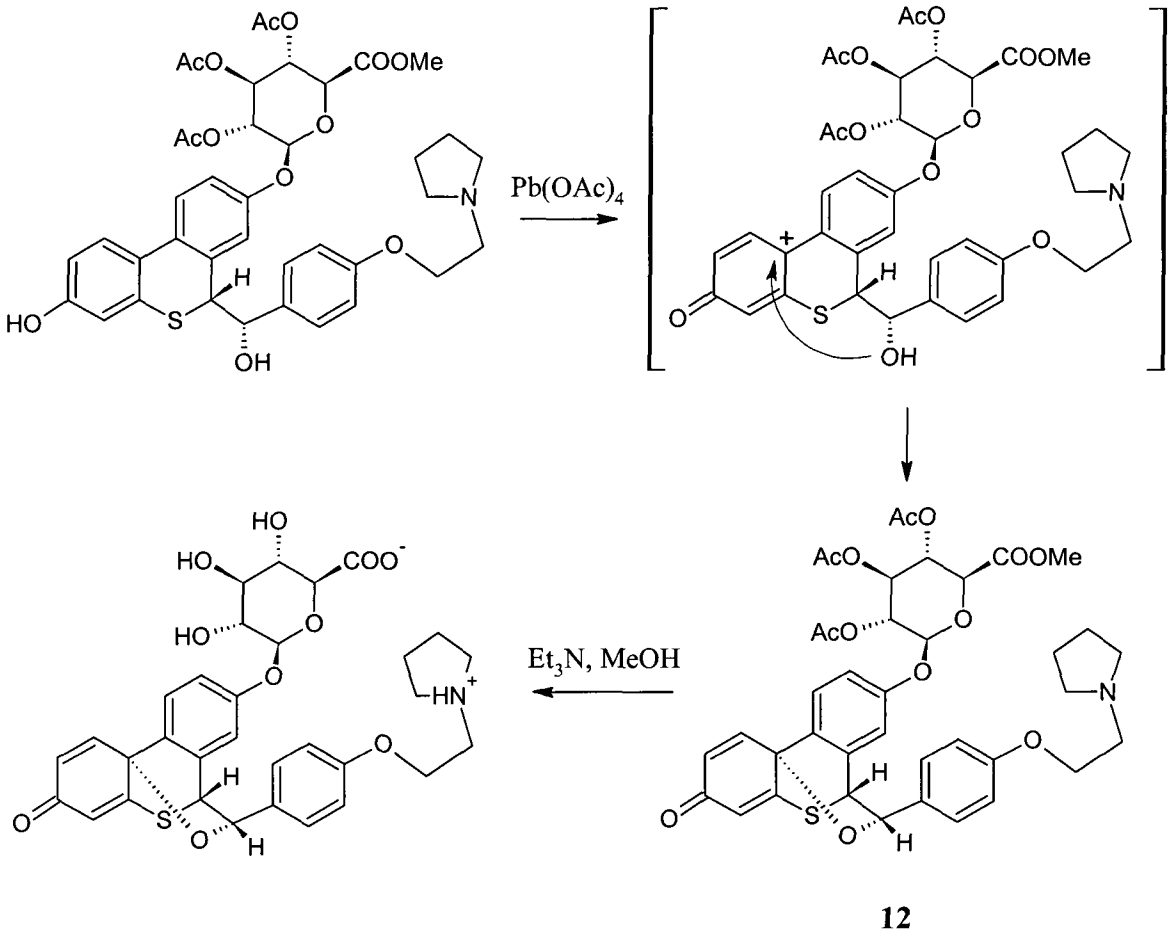
(+)-Maritidine

Scheme 2: Intramolecular oxidative coupling reaction generating 2,5-cyclohexadienone

Oxidative spiroannulation of phenols is an intramolecular ring formation via the transformation of functional groups. This is shown in the oxidation of tyrosine derivatives using a polymer supported hypervalent iodine reagent (diacetoxyiodo)benzene (PSDIB) to form spirolactones (**Scheme 4**).[24]

As can be seen from **Schemes 3** and **4**, there are only very little differences between coupling reactions and spiroannulation reactions. Nevertheless, for the remainder of this introduction, the focus will be on the formation of 2,5-cyclohexadienone structures, specifically p-quinols, via the oxidative spiroannulation of simple phenols.

There are several different types of oxidants used in the synthesis of spiro compounds. Common oxidants include hypervalent iodine (HVI) reagents, lead tetraacetate (LTA) and constant current electrochemical oxidation (CCE). The use of CCE or anodic



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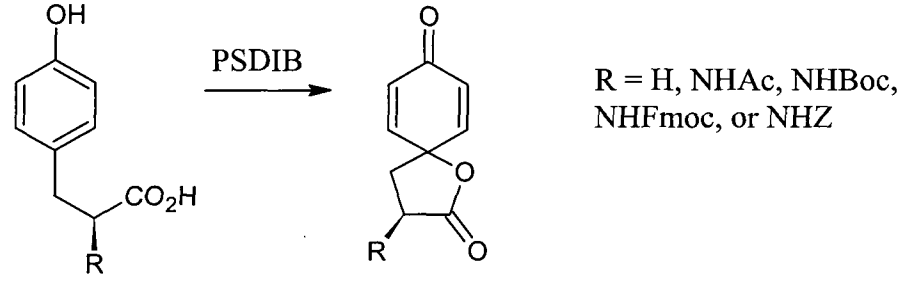
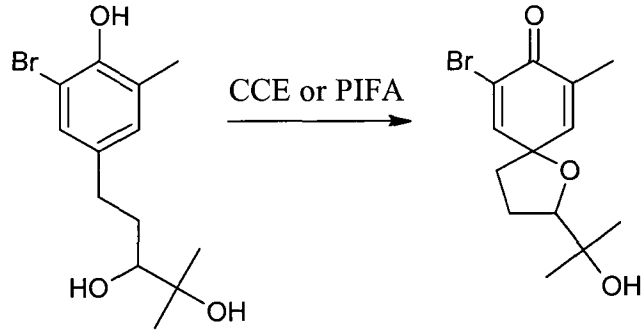
Scheme 3: Intramolecular oxidative coupling reaction generating 2,5-cyclohexadienone



Scheme 4: Oxidative cyclization or spiroannulation of phenols

oxidation has been the primary means of phenolic oxidation by the Nishiyama group in their study of the oxidation of monohalogenated phenols and the synthesis of Heliannuol derivatives.[18, 25-29] CCE is a safe alternative to heavy metal or explosive oxidants as this

process involves the passage of current (potentials of 1.07 - 1.64V) into an acidic or neutral electrolytic solution containing the phenol to be oxidized. However, this method often does not match the yields achieved when using other forms of oxidation. For example, Doi et al[28] found that oxidation of phenol **13** with PIFA gave the spirodienone **14** in 69% yield whereas CCE oxidation resulted in a percent yield of only 18%.

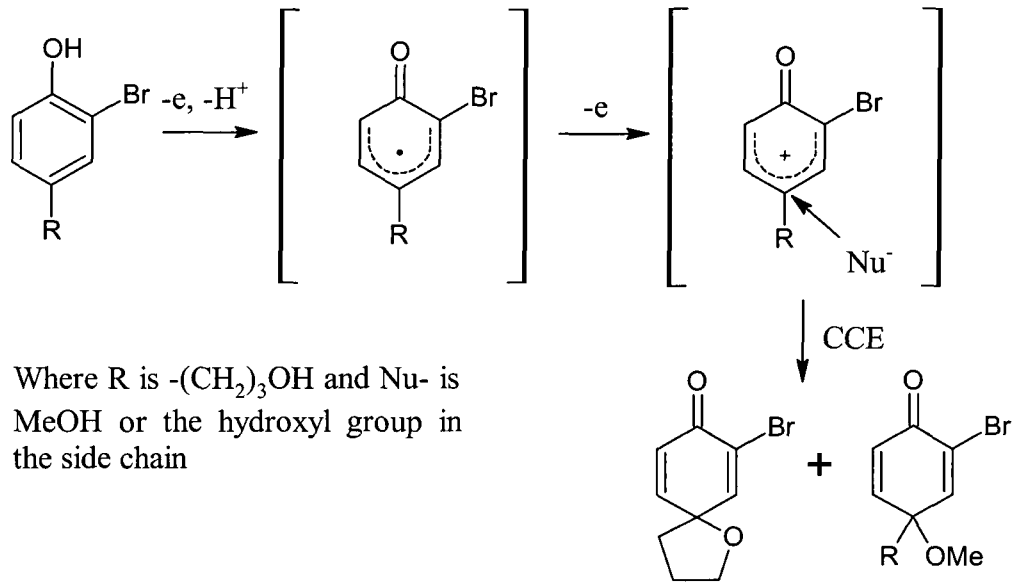


13 **14**

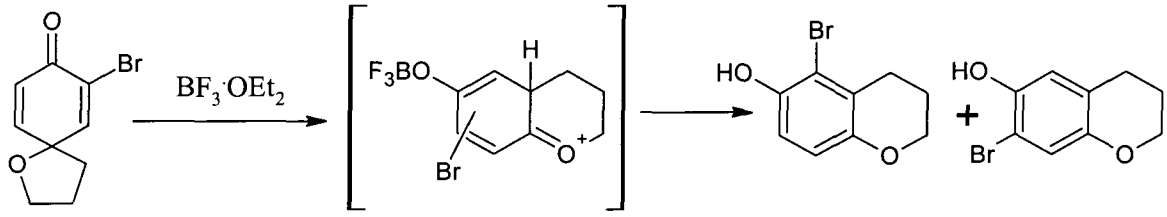
Scheme 5: Oxidation with either CCE or PIFA

In an earlier study, Mori et al[25] found that the steric hindrance of propyl or 3-hydroxypropyl substituents (i.e. elongation of the alkyl side chain in the para position of the phenolic hydroxyl) restricts intermolecular radical coupling reactions and instead resulted in the formation of dienone compounds. They proposed a plausible reaction process for the two electron oxidation products as shown in **Scheme 6**. These results enabled them to later describe the synthesis by anodic oxidation of several bicyclic-spiro compounds and their subsequent Lewis acid promoted rearrangement into dihydrobenzopyran-type structures as shown in **Scheme 7**.[26]

Another common oxidant used in the formation of 2,5-cyclohexadienone spiro compounds is LTA. This heavy metal based oxidant still finds use today, despite its toxicity.



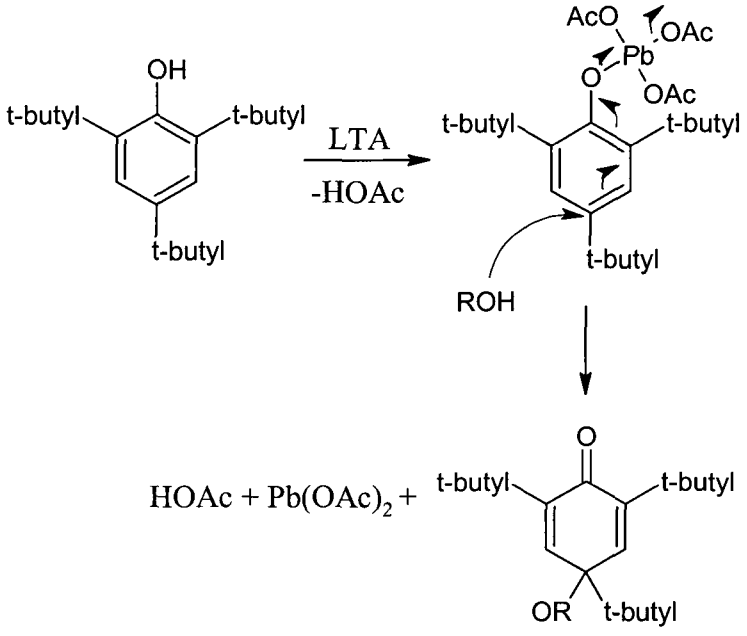
Scheme 6: Plausible reaction pathway for the formation of two electron oxidation products



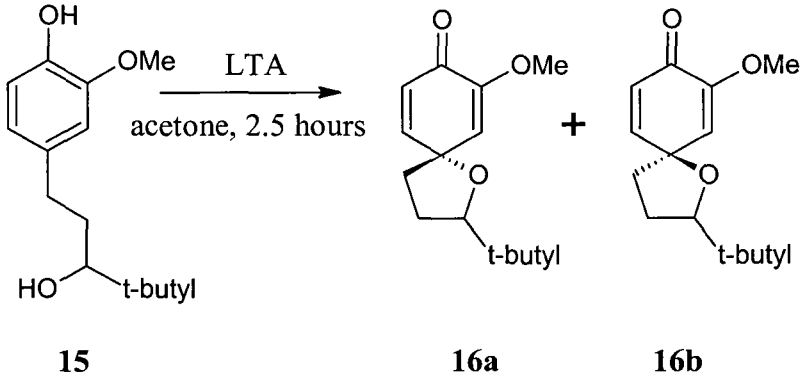
Scheme 7: Dihydrobenzopyran-type structures from a spiroether

The mechanism for the LTA mediated oxidation of phenols is believed to be an intramolecular concerted process (**Scheme 8**).[30]

Plourde utilized LTA in the diastereoselective oxidation of the phenol **15** in the formation of the spiroether **16a/16b**[6] shown in **Scheme 9**. By attaching the nucleophile as a tethered chain to the phenol at the para position, the formation of the para quinol is favoured. Furthermore, it was found that when the size of the alkyl moiety adjacent to the hydroxyl group was increased from an *iso*propyl group to a *t*-butyl group the diastereomeric ratio



Scheme 8: Mechanism of lead tetraacetate oxidation[30].



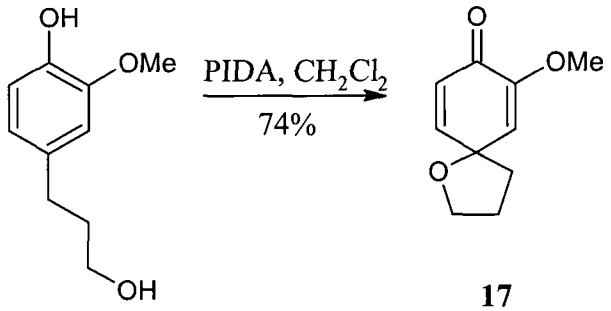
15 **16a** **16b**

Scheme 9: Diastereoselective synthesis of spiroethers using LTA

increased from 71/29 to 81/19. Neither the yield nor the diastereoselectivity were achieved when HVI reagents were employed which suggested a change in oxidant results in a different transition state for the formation of the spiroethers.

HVI reagents such as phenyliodine diacetate (PIDA), also known as iodobenzene diacetate or (diacetoxyiodobenzene) (DIB), and phenyliodinetrifluoroacetate (PIFA), also known as bis(trifluoroacetoxy)iodobenzene, are less toxic alternatives to heavy metal based reagents such as LTA. Oxidative cyclization products formed using HVI reagents include

spirolactams[31-39], spirolactones[40-44], and spiroethers[45-47]. Quideau et al[46] formed the spiroether **17** in 74% yield using PIDA in dichloromethane.



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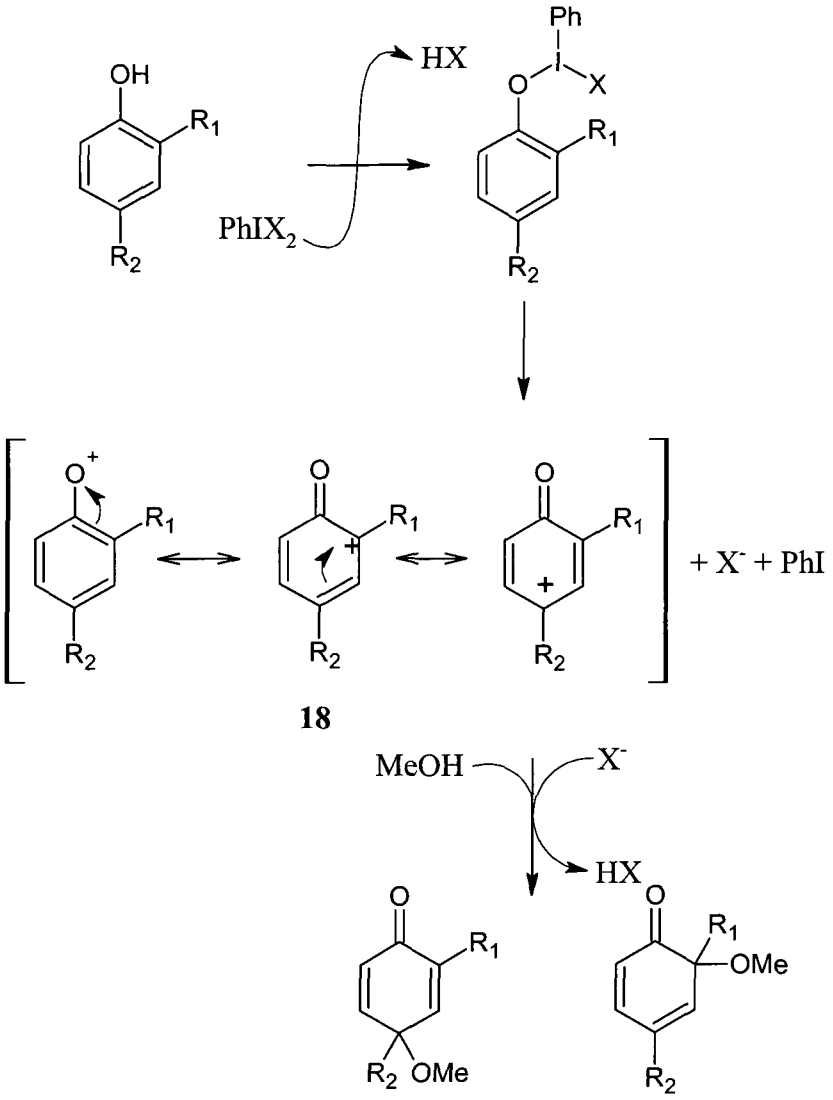
Scheme 10: Formation of a spiroether using PIDA

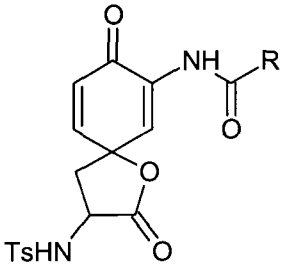
The mechanism of phenolic oxidation using HVI reagents is believed to proceed via a phenoxenium ion **18** as shown in **Scheme 11.**[48] In the oxidations examined by the Kurti group, it was found that there was a total lack of diastereo and enantioselectivity, thus giving support to the formation of the phenoxenium ion **18.**

The diastereoselective synthesis of spirolactones **19a** and **19b** (**Figure 9**) were accomplished using PIFA as the oxidant.[40] These spirolactones may be used as a precursor in the synthesis of analogs of the manumycin family of natural products. A mixture of diastereomers was obtained in approximately 3:1 ratio of which the major diastereomers (+)**19a** and (+)**19b** were isolated from the crude reaction mixtures in 41% and 43% yields respectively. The absolute configuration of the chiral spirocentres was found to be R for both compounds.[49]

As can be seen from the previous literature survey, the spiroannulation of simple phenols has been known for quite some time and can easily be accomplished under a variety of conditions. However, the diastereoselective version of the reaction is still problematic with only a few examples and generally weak to modest diastereoselectivity is obtained. To



Scheme 11: Mechanism of HVI reagent phenolic oxidation[48]



19a R=CH_3

19b R=C_6H_5

Figure 9: Spirolactones synthesized using PIFA as the oxidant

better understand the effect controlling the diastereoselectivity of these reactions and hopefully generate better results, i.e. higher diastereoselectivity, I studied the effect (if any) that would be generated by changing the size of the aromatic substituent located on carbon 3 of the aromatic ring (**Figure 3, 6a**). This appeared to be a logical step given that the stereoelectronic effect at the same position on the aromatic ring was also being studied in Dr. Plourde's laboratory. The results of this study are summarized in the next section.

Chapter 2

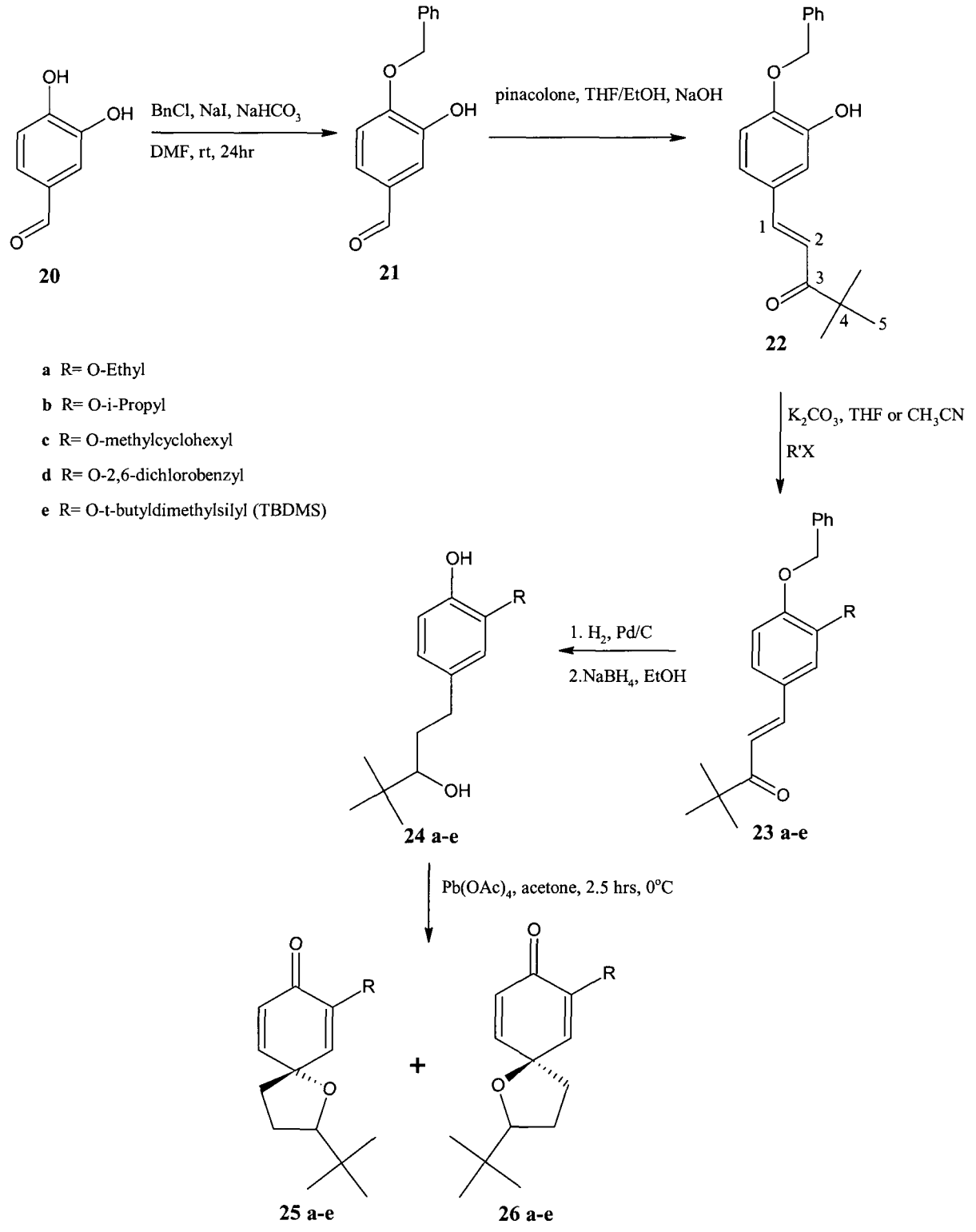
Results and Discussion

In order to study the effect steric hindrance has on the spiroannulation of phenols I needed to synthesize alcohols **24a-e**. The synthesis of these alcohols is summarized in **Scheme 12**. The selective protection of the 4-hydroxyl of 3,4-dihydroxy benzaldehyde **20** to form **21** followed a known procedure.[9] The yield of this protection ranged from 38-66%; which was lower than the reported yield of 70%. This lower yield may be due to the modification of the procedure to remove the DMF by successive extractions with 5% LiCl then 10% HCl instead of using a larger column to perform the chromatography. I also found that the crude product could be recrystallized from ethanol giving off white needle-like crystals.

The synthesis of **22** involved a condensation reaction between the aldehyde function of **21** and pinacolone (3,3-dimethyl-2-butanone) providing **22** in yields ranging from 57-79%. Examination of the ^{1}H-NMR spectrum proved that the reaction was a success. In addition to the loss of the aldehyde peak at 9.84 ppm, the peak at 1.22 ppm integrating for 9H corresponding to the t-butyl group of pinacolone illustrated that the condensation reaction occurred. Doublets at 6.95 ppm and 7.57 ppm having coupling constants of 15.5 Hz confirmed the trans relationship of the alkene protons H_1 and H_2.

The base catalyzed Williamson ether synthesis resulting in the substitution of the various R groups onto the free phenolic hydroxyl of **22** proceeded via an S_N2 mechanism. The loss of the hydroxyl peak at 5.71 ppm (also confirmed by IR spectroscopy) and the appearance of new signals in the ^{1}H-NMR spectra of **23a-e** confirmed that these ether

formations proceeded as expected. In the case of **23a**, a new triplet/quartet pattern typical



Scheme 12: Synthesis Reaction Scheme

of the ethyl group was observed at 1.49 (t) and 4.18 (q). Similarly, a typical doublet/multiplet coupling system of the isopropyl group was easily identified for **23b** at 1.37 (d) and 4.57 (m) ppm in its ^{1}H-NMR spectrum. The ^{1}H-NMR spectrum of **23c** showed the expected methylene protons at 3.86 ppm (d) as well as a multiplet integrating for 5H's at 1.83 ppm. The other protons of the cyclohexyl group were overlapping with the signal of the t-butyl group at ~ 1.2 ppm (see spectrum in **Appendix 1**). Compound **23e** was also easy to identify given the typical pattern of singlets integrating for 6 H's and 9 H's of the TBDMS function. These two new signals were found at 0.1 ppm (methyl) and 0.97 ppm (t-butyl). Only the dichlorobenzyl group (**23d**) was in anyway misleading as to the success of the reaction. There was only an increase in the multiplicity in the aromatic region of the ^{1}H NMR spectroscopy and the appearance of a new OCH_2 group, which on quick inspection still looked like the hydroxyl peak until the integration of the peaks was completed. It revealed that the singlet at 5.42 ppm was due to 2 protons while the aromatic region integrated for a total of 11 protons as expected for structure **23d**. **Table 1** summarizes the chemical shifts of these new groups for **23a-e**.

Table 1: Chemical shifts of alkyl groups

	23a	**23b**	**23c**	**23d**	**23e**
^{1}H-NMR Chemical Shifts (ppm)	1.49 (t, 3H, ethyl CH_3) 4.18 (q, 2H, ethyl CH_2)	1.37 (d, 6H, i-Pr CH_3) 4.57 (m, 1H, i-Pr CH)	1.83 (m, 5H, cyclohexyl) 3.86 (d, 2H, OCH_2)	5.42 (s, 2H, OCH_2) 7.30 (m, 11H, aromatic)	0.01 (s, 6H, Si-CH_3) 0.97 (s, 9H, TBDMS CH_3)

Table 2 summarizes the yields and physical appearance of the products **23a-e**. This step went particularly well for **23a** and **23b**. The crude products were 95+% pure based on ^{1}H-NMR spectroscopy so purification via column chromatography was not performed. For **23e**, I found that the TBDMSCl hydrolyzed quite easily while stored in the stock container despite flushing with nitrogen gas after each use. As a result, the quantities used in the reaction for **23e** were quite high and required multiple additions of reagents, both of TBDMSCl and pyridine, with several days of stirring at room temperature while monitoring via thin layer chromatography (tlc) for completion of the reaction. This procedure did result in the need to purify the product **23e** by chromatography and recycling the starting material **22** for further reaction. However, I was able to increase the yield by recovering and recycling **22**. The yield reported in **Table 2** and in the experimental section is after recovering **22** via column chromatography and re-reacting it. The formation of **23c** and **23d** required column chromatography to remove excess reagent from the reaction mixture and the formation of these two compounds generated lower yields.

Table 2: Summary of yields and physical appearances for **23a-e**

	23a	**23b**	**23c**	**23d**	**23e**
Percent Yield for step 22-23	94%	98%	70%	76%	83%
Appearance	Light yellow solid	Light yellow solid	Light yellow solid	Light yellow oil	Light yellow oil

The hydrogenation of **23a-e** was carried out under classic reaction conditions [H_2, 10% Pd/C, ethyl acetate, 30 psi]. This reaction had two distinct purposes: (1) the reduction of the alkene double bond of the para side chain in **23** and (2) the removal of the benzyl protecting group. As such, the reaction was easily followed to completion by tlc since removal of the benzyl

group would yield a phenol which would be expected to be more polar than **23**. Furthermore, the success of this reaction was also easy to confirm by ^{1}H-NMR spectroscopy since the two doublets of the alkene protons (usually ~ 7.0 and 7.6 ppm) of **23** as well as the benzylic methylene protons (~ 5.2 ppm) disappeared in the ^{1}H-NMR spectrum of the crude reaction mixture. I decided early on in the project to treat the crude hydrogenation products to the reduction conditions [$NaBH_4$, ethanol]. ^{1}H-NMR spectroscopy of my first reduction of **23a** showed that in addition to the expected removal of the benzyl protecting group and hydrogenation of double bond, a partial reduction of the carbonyl ketone was also occurring, but to a smaller extent. Column chromatography after hydrogenation resulted in the unnecessary loss of product and required combining fractions of the isolated reduction product at a later stage. The combined sequence of hydrogenation and sodium borohydride reduction produced clean products however in some cases (**24c-e**) the yields were unexpectedly low. Despite repeated rinsing during the Celite® filtration, the yield did not approach quantitative amounts as previously reported for similar compounds.[6] **Table 3** summarizes the results of the hydrogenation and reduction steps for the synthesis of **24a-e**.

Previous work performed in this laboratory suggested that the spiroannulation of similar phenolic derivatives gave the best diastereoselectivity at 0°C and using LTA as the oxidant.[6] To determine whether or not similar results would occur with these compounds, the effect of temperature was examined using LTA to form **25/26a** (**Table 4**). The alcohol **24a** was dissolved in acetone and stirred for 5 minutes at either room temperature, 0°C or -15°C after which LTA was added. The mixtures remained stirring at their respective temperatures for 2.5 hours after which time they were filtered through Celite®, ethylene

Table 3: Summary of yields for **24a-e**

	24a	**24b**	**24c**	**24d**	**24e**
Percent Yield for step 23-24	91%[a]	81%[a]	44%[a]	46%[a]	96%[b] 68%[a]
Appearance	Light yellow solid	Light yellow oil	Light yellow oil	Light yellow oil	Light yellow oil

[a]After purification by chromatography on silica gel using a mixture of ethyl acetate and hexanes as eluant in ratios described in the experimental section.
[b]Before purification.

glycol was added and allowed to stir overnight before an additional filtration through Celite®. ^{1}H-NMR spectroscopy of the crude mixtures showed that the diastereomeric ratio was the same at all three temperatures as shown in **Table 4**. The small differences between them were attributed to experimental error in determining these ratios. **Figure 10** is an expansion of the crude ^{1}H-NMR of **25/26a** at 0°C showing the signals for H_6. The diastereomeric ratio was determined by measuring the height of the integrals of the two signals and taking their sum. The integral height gives the relative area under the curve of the signals. The individual integral height of each doublet is then divided by the sum of the integral heights. In the case of **25/26a**, the sum was determined to be 178mm (integral height of doublet at 5.65 = 43mm, integral height of doublet at 5.75=135mm). Therefore, the signal at 5.65 is 24% of the total and the signal at 5.75 represents 76% of the sum, hence a diastereomeric ratio of 76/24. However, a significant improvement in yield was observed at 0°C (92%) versus 78% and 58% at room temperature and -15°C respectively. Based on this first series of results, it was decided to carry out all other spiroannulations at 0°C.

Table 4: Effect of temperature on spiroannulation of **24a** to **25/26a** using LTA

Temperature	Room temperature	0°C	-15°C
Mass LTA (2.5 eq.)	0.269 g	0.264 g	0.271 g
Purified mass	0.046g	0.054g	0.034g
% Yield	78	92	58
Diastereomer ratio using signals for H_6[a]	75/25	76/24	73/27

[a]Diastereomeric ratios were measured from the ^{1}H-NMR spectrum of the crude reaction mixture.

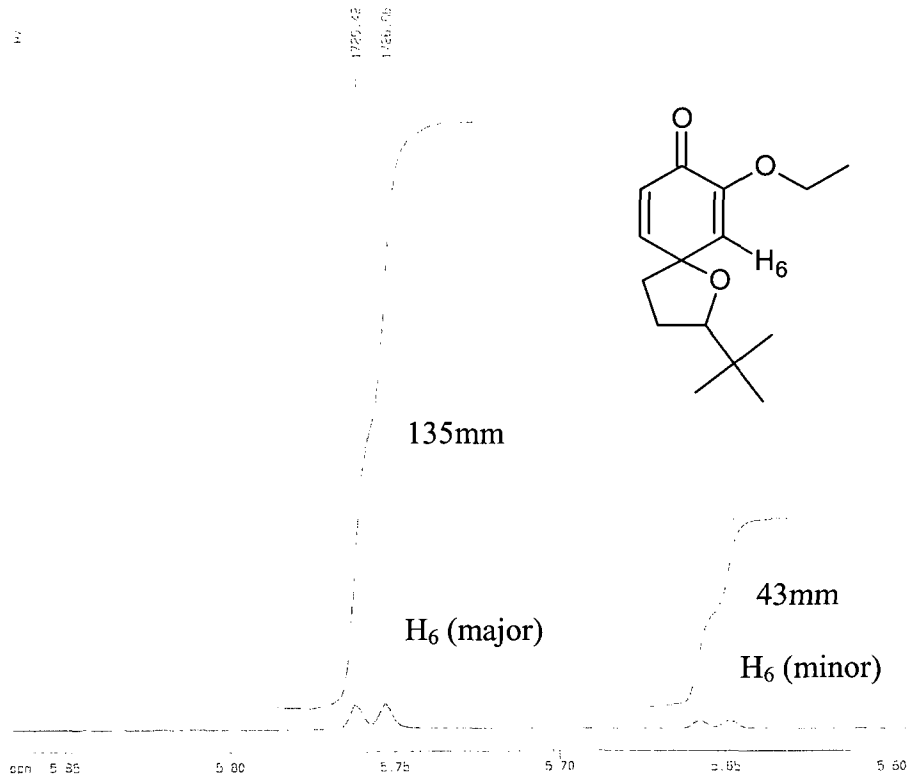


Figure 10: Expansion of ^{1}H-NMR of crude **25/26a** at 0°C

The choice of oxidant used in the spiroannulation was also examined, this time using the alcohol **24b**. There were three reasons why the alcohol **24b**, having a bulkier isopropyl R group was used rather than **24a**. Firstly, the temperature effect on the alcohol **24a** had

produced results similar to those previously published using a methyl group[6] so it was believed that similar results would occur with respect to the oxidant used.[6] Secondly, it was not known if the oxidant performance/mechanism would be affected by the size of the group. Thirdly and for more practical reasons, the previous investigation on temperature effects had severely depleted the stock of **24a** available. Solutions of **24b** in acetone were stirred at 0°C for 5 minutes prior to LTA and PIFA being added. The reactions were stirred at 0°C for 2.5 hours after which time the solution containing LTA was filtered through Celite®, ethylene glycol was added and allowed to stir overnight before an additional filtration through Celite®. To the solution containing PIFA was added distilled water and the mixture was extracted with ethyl acetate. The solution was dried with magnesium sulfate (anhydrous), filtered and evaporated in vacuo. As can be seen in **Table 5,** the diastereomeric ratio was significantly better with LTA (71/29) as the oxidant than when PIFA (50/50) was used. Similar observations were also reported from this laboratory for similar compounds.[6] While there are still no conclusions drawn to explain this fact, the answer may be associated with the differences in the mechanisms proposed for the oxidations using these reagents. Based on these preliminary results, it was decided that all other spiroannulations of compounds **24c-e** would be performed at 0°C using LTA as the oxidant.

Table 5: Effect of oxidant on spiroannulation of **24b** to **25/26b** at 0°C

Oxidant	LTA	PIFA
Equivalents used	3.5	1.1
Diastereomer ratio using signals for H_6[a]	71/29	50/50

[a]Diasteromeric ratios were measured from the ^{1}H-NMR spectrum of the crude reaction mixture.

Having optimized the reaction conditions in terms of oxidant and temperature to get maximum diastereoselectivity, I carried out the spiroannulations of the other alcohols, **24c-d**. The spiroannulation proceeded smoothly and in very good yield in the case of **24d**, giving **25/26d** in excellent yield (94%). However the reaction of **24c** afforded only 38% of **25/26c**. There is no apparent or logical reason for such a low yield since the alkyl substituent is similar in nature to the ethyl (**24a**) and the isopropyl (**24b**) groups used in the first two preliminary studies investigating the best temperature and oxidant to be used in these reactions.

I found that the diastereomeric ratio of the isomers did not increase as steric hindrance increased. In fact, both the ratio and yields actually decreased with increasing size of the alkyl group (**25/26a-d**) as seen in **Table 6**. I found that the best ratio (76/24) was for the ethyl group (**25/26a**), a similar ratio to that previously published for the methyl group (81/19).[6]

Table 6: Spiroannulation of **24a-e** to **25/26a-e** using LTA at 0°C

	25/26a	**25/26b**	**25/26c**	**25/26d**	**25/26e**
Diastereomeric ratio using signals for H_6[a]	76/24	71/29	65/35	51/49	n/a
δ (ppm) major:minor	5.76 : 5.65	5.77 : 5.67	5.74 : 5.62	6.00 : 5.89	n/a
Percent Yield[b]	92%	76%	38%	94%[a]	n/a

[a]Diasteromeric ratios were measured from the ^{1}H-NMR spectrum of the crude reaction mixture.
[b]Percent yield of combined isomers after purification by chromatography on silica gel using a mixture of ethyl acetate and hexanes as eluant in ratios described in the experimental section.

Of the five groups used, the TBDMS gave the most problems during the synthesis. I first experienced difficulty with this group while trying to purify **24e**. The TBDMS group

was labile in the slightly acidic environment of the silica gel. Using triethylamine (1%) in the eluant mixture prevented this from occurring in a second attempt and **24e** was isolated in 68% yield. Before using the triethylamine in the chromatography, I was able to synthesize **24e** in 96% yield. The purity of this (confirmed by ^{1}H-NMR spectroscopy) was such that I was able to use it in the next step without purification. The spiroannulation reaction did not go particularly well with the TBDMS group either. The diastereomeric ratio using the signals for H_6 in the ^{1}H-NMR spectra of the crude product **25/26e** was difficult to determine. It appeared as though the TBDMS group was unstable to the reaction conditions used, a conclusion that is based on a very populated ^{1}H-NMR spectrum. Quideau et al used a silyl enol ether carbon based nucleophile in the PIFA mediated oxidation of naphthols.[14] Perhaps the LTA promoted the cleavage of the oxygen - silicon bond.[14] Therefore, I decided to try to purify **25/26e** using column chromatography and use the ratios of the purified product for my analysis. Attempts at recovering **25/26e** failed despite using triethylamine in the solvent mixture. Boehlow et al[50] found that their spirocompound, a spiroisoxazoline, was sensitive to chromatography as well. They found that using a polymer supported (diacetoxyiodo)benzene (PSDIB would be equivalent to PSPIDA) gave excellent yield and purity with the workup requiring only filtration and eliminating the need for chromatography. This method might provide a means of synthesizing this spirocompound at a later date.

Chapter 3

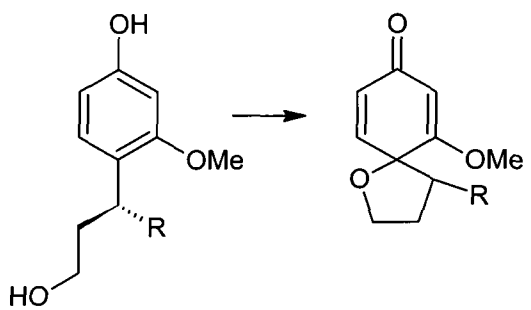
Conclusions

The syntheses of all intermediates and spirocompounds targeted at the outset of my project were carried out successfully providing four new spirocompounds not previously synthesized. The only exceptions being a low yield obtained for **25/26d** as well as the inability to prepare **25/26e** successfully. While I was able to prepare these compounds as diastereomeric mixtures, my results suggest that the size of the alkyl group located on C-3 of the aromatic ring does not positively affect the diastereoselectivity of the reactions. In fact, I found that increasing the size of the alkyl group had a negative impact on the diastereoselectivity decreasing from 74/26 to 65/35 from ethyl to methylcyclohexyl respectively.

It is unclear why the 2,6-dichlorobenzyl derivative gave spiroannulation products but no selectivity. The reason may be related to the electronic nature of this group rather than steric factors. A similar result has been observed in this laboratory when the aromatic ring is substituted with a chlorine at the 3-position of the ring. Spiroannulation takes place but without any selectivity.[10]

The fact that the ratios did not improve with increasing steric factors provides evidence that the spiroannulation is not affected by the size of the group attached at the 3-position. Instead, it gives supporting evidence that the stereoelectronic effect and location of the substituent has greater effect to the overall outcome of the reaction. Previous studies have shown that for the synthesis of (±)-2-tert-butyl-6-methoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one (**Scheme 1**), there was no diastereoselectivity in the reaction and yield was only

moderate at 45%.[13] This could be due to the fact that the t-butyl group and the OMe function were too far apart. This is also the case in my study. Moving the chiral element to a position adjacent to the site of the reaction as shown in **27 (Scheme 13)**, may provide more steric hindrance, and potentially a better diastereoselectivity in the spiroannulation reaction may result due to the steric factor created by the proximity of the two groups.



27

Scheme 13: A possible scenario to improve diastereoselectivity

Chapter 4

Experimental

All chemicals and solvents were used without further purification. Thin layer chromatography (tlc) was performed on silica gel coated aluminum plates from Silicycle (60Å, indicator F-254, thickness 250μm). Visualization of the tlc plates was accomplished with UV light (short wave UV, 254 nm) and by staining with Vanillin. Flash column chromatography was carried out using Silicycle silica gel (230-400 mesh, 60Å). Melting points were determined on a hot stage instrument and are uncorrected. Infrared (IR) were recorded neat on a Perkin Elmer System 2000 FTIR. Mass spectra were recorded with a Hewlett Packard 5989 B mass spectrometer (MS) with a 5890 Series II Gas Chromatograph (GC). ^{1}H (300.13MHz) and ^{13}C (75.47MHz) NMR spectra were recorded on a Bruker AMX300 spectrometer. All samples were dissolved in deuterated chloroform and the chemical shifts are expressed in parts per million (ppm) using tetramethylsilane (TMS) as internal standard.

(1E)-1-[4-(benzyloxy)-3-hydroxyphenyl]-4,4-dimethylpent-1-en-3-one **(22):**

To a solution of **21** (1.612 g, 7.07 mmol) in tetrahydrofuran (75 mL) and ethanol (75 mL) was added sodium hydroxide (0.864 g, 21.6 mmol, 3.06 eq.) and pinacolone (3.119 g, 31.2 mmol, 4.41 eq.). The mixture was left to reflux overnight. After 24 hours, a tlc of the reaction mixture confirmed the reaction had not gone to completion. Additional quantities of sodium hydroxide (0.754g, 18.9 mmol, 2.67 eq) and pinacolone (3.086g, 30.9 mmol, 4.36 eq) were added and the mixture was again refluxed overnight. The resulting dark reddish brown solution was cooled, acidified (10% HCl, 150 mL), concentrated *in vacuo* and extracted with dichloromethane (4 x 50 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a light amber oil that solidified upon standing. Chromatography (15%EtOAc/Hexanes) resulted in a clear amber oil which solidified to a light yellow solid overnight (1.722g, 79% yield).

IR (neat) cm^{-1}: 3406 (OH), 1673 (CO)

^{1}H-NMR ($CDCl_3$) δ: 1.22 (s, 9H, t-Bu CH_3), 5.15 (s, 2H, OCH_2), 5.71 (s, 1H, OH), 6.99 (d, 1H, J=15.5 Hz, H_2), 7.24 (m, 8H, aromatic), 7.59 (d, 1H, J=15.5Hz, H_1)

^{13}C-NMR ($CDCl_3$) δ: 26.8 (t-Bu CH_3), 43.6 (C_4), 71.5 (O-CH_2), 112.3 (Ar-C_2), 113.4 (Ar-C_5), 119.6 (C_2), 122.8 (Ar-C_6), 128.3 (Ar-$C_{2'}$,Ar-$C_{6'}$), 129.0 (Ar-$C_{4'}$), 129.2 (Ar-$C_{3'}$,Ar-$C_{5'}$), 137.0 (Ar-C_1), 143.0 (C_1), 146.4 (Ar-C_4), 148.0 (Ar-C_3), 204.7 (CO)

GCMS m/z (relative%): 310 (17), 251 (100), 219 (51), 162 (22), 91 (36), 57 (58)

Melting point: 92-93°C

1-(4-benzyloxy-3-ethoxyphenyl)-4,4-dimethyl-1-penten-3-one **(23a):**

To a solution of **22** (0.449 g, 1.45 mmol) in acetonitrile (30 mL) was added iodoethane (0.795 g, 5.10 mmol, 3.52 eq.) and potassium carbonate (0.692 g, 5.00 mmol, 3.45 eq.). The mixture was left to reflux overnight. The solution was cooled, washed with distilled water (30 mL), concentrated *in vacuo* and extracted with dichloromethane (3 x 20 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a light amber oil that solidified upon standing. The crude product was determined to be 95%+ pure by ^{1}H-NMR spectroscopy, therefore no chromatography was performed. The crude oil was left connected to a vacuum pump overnight to yield a light yellow solid (0.462 g, 94% yield).

IR (neat) cm^{-1}: 1678 (CO)

^{1}H-NMR ($CDCl_3$) δ: 1.22 (s, 9H, t-Bu CH), 1.49 (t, 3H, ethyl CH_3), 4.18 (q, 2H, ethyl CH_2), 5.19 (s, 2H, OCH_2), 7.04 (d, 1H, J=15.6 Hz, H_1), 7.24 (m, 9H, aromatic), 7.59 (d, 1H, J=15.5Hz, H_2)

^{13}C-NMR ($CDCl_3$) δ: 15.1 (ethyl CH_3), 26.6 (t-Bu CH_3), 65.1 (ethyl CH_2), 71.1 (O-CH_2), 113.2 (Ar-C_5), 114.4 (Ar-C_2), 118.9 (C_2), 122.6 (Ar-C_6), 127.3 (Ar- $C_{2'}$,Ar-$C_{6'}$), 128.1 (Ar-$C_{4'}$), 128.8 (Ar- $C_{3'}$,Ar-$C_{5'}$), 137.0 (Ar-$C_{1'}$), 143.1 (C_1), 149.4 (Ar- C_3), 150.8 (Ar- C_4), 204.4 (CO)

GCMS m/z (relative %): 338(100), 281(56), 191(18), 91(8)

Melting point: 88-91°C

1-(4-benzyloxy-3-isopropoxyphenyl)-4,4-dimethyl-1-penten-3-one **(23b):**

To a solution of **22** (0.437 g, 1.41 mmol) in acetonitrile (30 mL) was added 2-bromopropane (0.638 g, 5.19 mmol, 3.68 eq.) and potassium carbonate (0.711 g, 5.14 mmol, 3.65eq.). The mixture was left to reflux overnight. The cooled solution was washed with distilled water (30 mL), concentrated *in vacuo* and extracted with dichloromethane (3 x 20 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a dark amber oil. The crude product was determined to be 95%+ pure by ^{1}H-NMR spectroscopy, therefore no chromatography was performed. The crude oil was left connected to a vacuum pump overnight to yield a clear yellow oil which solidified after removing sample for analysis (0.486 g, 98% yield).

IR (neat) cm^{-1}: 1678 (CO)

^{1}H-NMR ($CDCl_3$) δ: 1.22 (s, 9H, t-Bu), 1.37 (d, 6H, J=6.2 Hz, i-Pr CH_3), 4.57 (m, 1H, i-Pr CH), 5.17 (s, 2H, OCH_2), 6.97 (d, 1H, J=15.5Hz, H_1), 7.30 (m, 8H, Ar), 7.60 (d, 1H, J=15.5 Hz, H_2)

^{13}C-NMR ($CDCl_3$) δ: 22.4 (i-Pr CH_3), 26.6 (t-Bu CH_3), 43.4 (C_4), 71.1 (OCH_2), 72.7 (i-Pr CH), 114.8 (Ar-C_5), 117.6 (Ar-C_2), 119.0 (C_2), 123.1 (Ar-C_6), 127.3 (Ar-$C_{2'}$, Ar-$C_{6'}$), 128.1 (Ar-$C_{4'}$), 128.8 (Ar-$C_{3'}$, Ar-$C_{5'}$), 137.1 (Ar-$C_{1'}$), 143.0 (C_1), 148.2 (Ar-C_3), 152.2 (Ar-C_4), 204.2 (CO)

GCMS m/z (relative %): decomposed

Melting point: 59-61°C

1-(4-benzyloxy-3-methylcyclohexyloxyphenyl)-4,4-dimethyl-1-penten-3-one **(23c):**

To a solution of **22** (0.275 g, 0.886 mmol) in acetonitrile (30 mL) was added bromo methyl cyclohexane (0.491 g, 2.77 mmol, 3.12 eq.) and potassium carbonate (0.692 g, 5.00 mmol, 5.64 eq.). The mixture was left to reflux overnight. The solution was cooled, washed with distilled water (30 mL), concentrated *in vacuo* and extracted with dichloromethane (3 x 20 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a light amber oil that solidified upon standing. Column chromatography on silica gel (10% EtOAc/hexanes) afforded a light yellow solid (0.251 g, 70%).

IR (neat) cm^{-1}: 1678 (CO)

^{1}H-NMR ($CDCl_3$) δ: 1.22 (s, 9H, t-Bu CH_3), 1.0-1.45 (m, 6H, cyclohexyl), 1.83 (m, 5H, cyclohexyl), 3.86 (d, 2H, J=6.02 Hz,cyclohexyl OCH_2), 5.15 (s, 2H, $BzOCH_2$), 6.97 (d, 1H, J=15.5Hz, H_1), 7.30 (m, 8H, Ar), 7.61 (d, 1H, J=15.5Hz, H_2)

^{13}C-NMR ($CDCl_3$) δ: 26.1 (cyclohexyl C_3, cyclohexyl C_5), 26.7 (t-Bu C_5), 30.1 (cyclohexyl C_2, cyclohexyl C_6), 37.9 (cyclohexyl C_1), 43.3 (C_4), 71.2 ($BzOCH_2$), 75.0 (OCH_2cyclohexyl), 113.3 (Ar-C_5), 114.7 (Ar-C_2), 118.9 (C_2), 122.5 (Ar-C_6), 127.3 (Ar-$C_{2'}$, Ar-$C_{6'}$), 128.1 (Ar-$C_{4'}$), 128.7 (Ar-$C_{3'}$, Ar-$C_{5'}$), 137.2 (Ar-$C_{1'}$), 143.3 (C_1), 149.9 (Ar-C_4), 150.9 (Ar-C_3), 204.4 (C_3)

GCMS m/z (relative %): 406 (83), 349 (100), 318 (23), 253 (28), 220 (33), 91, (10), 57 (8)

Melting point: 103-105°C

1-(4-benzyloxy-3-(2,6-dichlorobenzyloxy)-4,4-dimethyl-1-penten-3-one **(23d):**

To a solution of **22** (0.450 g, 1.45mmol) in acetonitrile (30 mL) was added 2,6-dichlorobenzyl bromide (0.731 g, 3.05 mmol, 2.10 eq.), sodium iodide (0.055 g, 0.37 mmol, 0.25 eq.) and potassium carbonate (0.825 g, 5.97 mmol, 4.12 eq.).The mixture was refluxed overnight. The solution was cooled, washed with distilled water (30 mL), concentrated *in vacuo* and extracted with dichloromethane (3 x 20 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a clear yellow oil. Chromatography on silica gel (10% EtOAc/hexanes) afforded a clear fluorescent like yellow oil (0.568 g, 84%).

IR (neat) cm^{-1}: 1678 (CO)

^{1}H-NMR ($CDCl_3$) δ: 1.23 (s, 9H, t-butyl CH_3), 5.17 (s, 2H, OCH_2), 5.42 (s, 2H, OCH_2), 6.98 (d, 1H, J=15.6Hz, H_1), 7.30 (m, 11H, Ar), 7.60 (d, 1H, J=15.6Hz, H_2)

^{13}C-NMR ($CDCl_3$) δ: 26.6 (C_5), 43.4 (C_4), 67.3 ($DiClBzOCH_2$), 71.3 ($BzOCH_2$), 114.9 (Ar-C_5), 115.9 (Ar-C_2), 119.2 (C_2), 124.2 (Ar-C_6), 127.5 (Ar- $C_{2'}$,Ar-$C_{6'}$), 128.1 (Ar-$C_{4'}$), 128.7 (Ar- $C_{3'}$,Ar-$C_{5'}$), 130.0 ($DiClBzC_3$, $DiClBzC_5$), 130.6 ($DiClBzC_4$), 132.5 ($DiClBzC_2$, $DiClBzC_6$), 136.9 ($DiClBzC_1$), 137.3 (Ar- $C_{1'}$), 142.8 (C_1), 149.1 (Ar- C_3), 151.8 (Ar- C_4), 204.4 (C_3)

GCMS m/z (relative %): decomposed

1-(4-benzyloxy-3-t-butyldimethylsilyloxy)-4,4-dimethyl-1-penten-3-one **(23e):**

To a solution of **22** (0.258 g, 0.831 mmol) in dichloromethane (30 mL) was added pyridine (0.262 g, 3.31 mmol, 3.98 eq) and t-butyldimethylsilyl chloride (TBDMSCl) (0.347 g, 2.30 mmol, 2.77 eq). The mixture was left to stir overnight. The solution was acidified (10%

HCl) and extracted with dichloromethane (3 x 20 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a light yellow oil. Chromatography on silica gel (20% EtOAc/hexanes) afforded a light yellow oil which crystallized on the vacuum pump. (0.138g, 38.9% yield). To improve the yield, the unreacted starting material was recovered from the column and rereacted with pyridine (0.128g) and TBDMSCl (0.243g). After chromatography, an additional 0.157g product was recovered (83.3% total yield).

IR (neat) cm^{-1}: 1681

^{1}H-NMR ($CDCl_3$) δ: 0.098 (s, 6H, Si-CH_3), 0.968 (s, 9H, TBDMS CH_3), 1.22 (s, 9H, t-Bu CH_3), 5.08 (s, 2H, O-CH_2), 6.95 (d, 1H, J=15.6 Hz, H_1), 7.40 (m, 8H, aromatic) 7.56 (d, 1H, J=15.6 Hz, H_2)

^{13}C-NMR ($CDCl_3$) δ: -4.44 (Si-CH_3), 18.58 (TBDMS Si-C), 25.87 (t-Bu CH_3), 26.65(TBDMS CH_3), 70.91(O-CH_2), 113.6 (Ar-C_5), 118.8 (Ar-C_2), 120.8(Ar-C_6), 122.9 (Ar-$C_{1'}$), 128.0 (Ar-$C_{2'}$, Ar-$C_{6'}$), 128.3 (Ar-$C_{4'}$), 128.4 (Ar-C_1), 128.7 (Ar-$C_{3'}$, Ar-$C_{5'}$), 136.6 (C_1), 142.9 (Ar-C_3), 152.4 (Ar-C_4), 204.4 (CO)

GCMS m/z (relative %): 425 (78), 367 (100), 277 (28), 219 (78), 111 (6), 57 (9)

(±)-1-(3-ethoxy-4-hydroxyphenyl)-4,4-dimethyl-3-pentanol **(24a):**

To a solution of **23a** (0.408 g, 1.21 mmol) in ethyl acetate (30 mL) was added 5% palladium over carbon (0.235 g) and the mixture was agitated in an hydrogenator under an atmosphere of H_2 overnight. The mixture was filtered through Celite®, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a clear yellow oil. ^{1}H-NMR of the crude product

confirmed the removal of the benzyl protecting group, reduction of the double bond and the partial reduction of carbonyl group.

To a solution of the crude hydrogenation product (0.298 g, 1.19 mmol) in ethanol (30 mL) was added sodium borohydride (0.144 g, 3.81 mmol, 3.20 eq.). The resulting mixture was allowed to stir at room temperature for 3 hours. The solution was acidified (10% HCl, 20 mL) and allowed to stir over night. The solution was condensed *in vacuo*, washed with water (10 mL) and extracted with dichloromethane (3 x 25 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo*. Chromatography on silica gel (20% EtOAc/hexanes) gave a viscous clear light yellow oil which partially solidified after being connected to a vacuum pump over night (0.274 g, 90% yield)

IR (neat) cm^{-1}: 3422 (OH)

^{1}H-NMR ($CDCl_3$) δ: 0.89 (s, 9H, t-butyl), 1.44 (t, 3H, ethyl CH_3), 1.54 (m, 1H, H_{2a}), 1.61 (broad s, 1H, OH), 1.80 (m, 1H, H_{2b}), 2.54 (m, 1H, H_{1a}), 2.85 (m, 1H, H_{1b}), 3.22 (broad d, 1H, J=10.5Hz, H_3), 4.10 (q, 2H, ethyl CH_2), 5.54 (s, 1H, exchangeable with D_2O, OH), 6.71 (m, 2H, ArH_2 and ArH_6), 6.84 (d, 1H, J=8.6Hz, ArH_5)

^{13}C-NMR ($CDCl_3$) δ: 15.1 (ethyl CH_3), 25.9 (t-butyl CH_3), 33.3 (C_1), 33.9 (C_4), 35.1 (C_2), 79.6 (C_3), 112.2 (ArC_2), 114.4 (ArC_5), 121.0 (ArC_6), 134.5 (ArC_1), 144.0 (ArC_4), 145.8 (ArC_3)

GCMS m/z (relative %): 252 (100), 165 (19), 151 (37)

(±)1-(4-hydroxy-3-isopropylphenyl)-4,4-dimethyl-3-pentanol **(24b):**

To a solution of **23b** (0.424 g, 1.20 mmol) in ethyl acetate (30 mL) was added 5% palladium over carbon (0.270 g) and the mixture was agitated in an hydrogenator under an atmosphere of H_2 overnight. The mixture was filtered through Celite®, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a clear yellow oil. ^{1}H-NMR of the crude product confirmed the removal of the benzyl protecting group, reduction of the double bond and the partial reduction of carbonyl group.

To a solution of the crude hydrogenation product (0.306 g, 1.16 mmol) in ethanol (30 mL) was added sodium borohydride (0.118 g, 3.12 mmol, 2.69 eq.). The resulting mixture was allowed to stir at room temperature for 3 hours. The solution was acidified (10% HCl, 20 mL) and allowed to stir over night. The solution was condensed *in vacuo*, washed with distilled water (10 mL) and extracted with dichloromethane (3 x 25mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo*. Chromatography on silica gel (10% EtOAc/hexanes) gave a clear light yellow oil after being connected to a vacuum pump overnight (0.260 g, 81% yield).

IR (neat) cm^{-1}: 3420 (OH)

^{1}H-NMR ($CDCl_3$) δ: 0.89 (s, 9H, t-butyl), 1.36 (dd, 6H, J=2.3, 6.2Hz, i-Pr CH_3), 1.54 (m, 1H, H_{2a}), 1.67 (broad s, 1H, OH), 1.80 (m, 1H, H_{2b}), 2.53 (m, 1H, H_{1a}), 2.83 (m, 1H, H_{1b}), 3.21 (broad d, 1H, J=10.8Hz, H_3), 4.58 (m, 1H, i-Pr CH), 5.60 (s, 1H, exchangeable with D_2O, OH), 6.71 (m, 2H, ArH_2 and ArH_6), 6.84 (d, 1H, J=7.95Hz, ArH_5)

^{13}C-NMR ($CDCl_3$) δ: 22.5 (i-Pr CH_3), 25.9 (t-butyl CH_3), 33.2 (C_1), 33.9 (C_4), 35.1 (C_2), 71.8 (i-Pr CH), 79.5 (C_3), 113.9 (ArC_5), 114.5 (ArC_2), 121.2 (ArC_6), 134.4 (ArC_1), 144.0 (ArC_4)

GCMS m/z (relative %): 266 (100), 249 (35), 205 (8), 165 (33), 123 (44)

(±)-1-(4-hydroxy-3-methylcyclohexyloxy)-4,4-dimethyl-3-pentanol **(24c):**

To a solution of **23c** (0.220 g, 0.541 mmol) in ethyl acetate (30 mL) was added 5% palladium over carbon (0.118 g) and the mixture was agitated in an hydrogenator under an atmosphere of H_2 overnight. The mixture was filtered through Celite®, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a light amber oil. ^{1}H-NMR of the crude product confirmed the removal of the benzyl protecting group, reduction of the double bond and the partial reduction of carbonyl group.

To a solution of the crude hydrogenation product (0.174 g, 0.547 mmol) in ethanol (30 mL) was added sodium borohydride (0.061 g, 1.61 mmol, 2.94 eq.). The resulting mixture was allowed to stir at room temperature for 3 hours. The solution was acidified (10% HCl, 20 mL) and allowed to stir over night. The solution was condensed *in vacuo*, washed with water (10 mL) and extracted with dichloromethane (3 x 25 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo*. Chromatography on silica gel (20% EtOAc/hexanes) gave a clear light yellow oil after being connected to a vacuum pump overnight (0.074 g, 43% yield).

IR (neat) cm^{-1}: 3419 (OH)

^{1}H-NMR ($CDCl_3$) δ: 0.89 (s, 9H, t-Bu CH_3), 1.0-1.8 (m, 11 H, cyclohexyl), 2.54 (m, 1H, H_{1a}), 2.83 (m, 1H, H_{1b}), 3.22 (broad d, 1H, J=10.5Hz, H_3), 3.82 (d, 2H, OCH_2), 5.53 (s, 1H, exchangeable with D_2O, OH), 6.71 (m, 2H, ArH_2 and ArH_6), 6.84 (d, 1H, J=8.5Hz, ArH_5)

^{13}C-NMR ($CDCl_3$) δ: 25.89 (t-Bu CH_3), 25.96 ($C_{3'}$ $C_{5'}$), 26.7 ($C_{4'}$), 30.1 ($C_{2'}$ $C_{6'}$), 33.3 (C_1), 33.9 (C_4), 35.1 (C_2), 37.9 ($C_{1'}$), 74.4 (OCH_2), 79.6 (C_3), 112.1 (ArC_2), 114.3 (ArC_5), 120.9 (ArC_6), 134.5 (ArC_1), 144.0 (ArC_4), 146.1 (ArC_3)

GCMS m/z (relative %): 319 (100), 218 (21), 123 (16)

(±)-1-(3-(2,6-dichlorobenzyloxy)-4-hydroxy)-4,4-dimethyl-3-pentanol **(24d):**

To a solution of **23d** (0.534 g, 1.14 mmol) in ethyl acetate (30 mL) was added 5% palladium over carbon (0.373 g) and the mixture was agitated in an hydrogenator under an atmosphere of H_2 overnight. The mixture was filtered through Celite®, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a clear yellow oil. ^{1}H-NMR of the crude product confirmed the removal of the benzyl protecting group, reduction of the double bond and the partial reduction of carbonyl group.

To a solution of the crude hydrogenation product (0.423 g, 1.11 mmol) in ethanol (30 mL) was added sodium borohydride (0.187g, 4.94 mmol, 4.45 eq.). The resulting mixture was allowed to stir at room temperature for 3.5 hours. The solution was acidified (10% HCl, 20 mL) and allowed to stir over night. The solution was condensed *in vacuo*, washed with water (10 mL) and extracted with dichloromethane (3 x 25 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo*. Chromatography on silica gel (25% EtOAc/hexanes) gave a clear light yellow oil after being connected to a vacuum pump overnight (0.198 g, 46% yield after two steps).

IR (neat) cm^{-1}: 3397 (OH)

^{1}H-NMR ($CDCl_3$) δ: 0.92 (s, 9H, t-Bu), 1.57 (m, 1H, H_{2a}), 1.85 (m, 1H, H_{2b}), 2.61 (m, 1H, H_{1a}), 2.85 (m, 1H, H_{1b}), 3.25 (broad d, 1H, J=10.4Hz, H_3), 5.35 (s, 2H, OCH_2), 5.69 (s, 1H, exchangeable with D_2O, OH), 6.85 (m, 3H, Ar), 7.35 (m, 3H, diClBz)

^{13}C-NMR ($CDCl_3$) δ: 25.9 (t-butyl CH_3), 33.2 (C_1), 33.9 (C_4), 35.1 (C_2), 66.6 (OCH_2), 79.6 (C_3), 113.8 (ArC_2), 114.9 (ArC_5), 122.3 (ArC_6), 128.8 ($DiClBzC_3$, $DiClBzC_5$), 130.9 ($DiClBzC_4$), 132.0 ($DiClBzC_2$, $DiClBzC_6$), 134.6 (ArC_1), 137.1 ($DiClBzC_1$), 144.6 (ArC_4), 145.5 (ArC_3)

GCMS m/z (relative %): 382 (63), 365 (100), 282 (17), 219 (7)

(±)-1-(3-t-butyldimethylsilyloxy)-4-hydroxy)-4,4-dimethyl-3-pentanol **(24e):**

To a solution of **23e** (0.243 g, 0.572 mmol) in ethyl acetate (30 mL) was added 5% palladium over carbon (0.173 g) and the mixture was agitated in an hydrogenator under an atmosphere of H_2 overnight. The mixture was filtered through Celite®, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo* to give a clear yellow oil. ^{1}H-NMR of the crude product confirmed the removal of the benzyl protecting group, reduction of the double bond and the partial reduction of carbonyl group.

To a solution of the crude hydrogenation product (0.178 g, 0.535 mmol) in ethanol (30 mL) was added sodium borohydride (0.056g, 1.48 mmol, 2.77 eq). The resulting mixture was allowed to stir at room temperature for 2.5 hours. The solution was acidified (10% HCl), condensed *in vacuo*, and extracted with dichloromethane (3 x 25 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and the solvent was evaporated *in vacuo*. ^{1}H-NMR of crude sample was very clean so no chromatography was performed. (0.172g, 96% yield after two steps.)

Note: Chromatography on silica gel (25% EtOAc/1% Et_3N/hexanes) was performed on a small sample (48mg) with little difference in purity (as per ^{1}H-NMR). However, I lost 16mg of sample in the process (48 mg to 32 mg).

IR (neat) cm^{-1}: 3335 (OH)

^{1}H-NMR ($CDCl_3$) δ: 0.26 (s, 6H, Si-CH_3), 0.88 (s, 9H, TBDMS CH_3), 1.01 (s, 9H, t-butyl), 1.55 (m, 1H, H_{2a}), 1.60 (broad s, 1H, OH), 1.76 (m, 1H, H_{2b}), 2.53 (m, 1H, H_{1a}), 2.76 (m, 1H, H_{1b}), 3.21 (broad d, 1H, J=10.4Hz, H_3), 5.38 (d, 1H, OH), 6.68 (m, 3H, aromatic)

^{13}C-NMR ($CDCl_3$) δ: -4.05 (TBDMS Si-CH_3), 18.4 (TBDMS Si-C), 25.8 (TBDMS t-butyl CH_3), 25.9 (t-butyl CH_3), 32.8 [32.9] (C_1), 33.5 [33.6] (C_4), 35.1 (C_2), 79.5 (C_3), 114.8 (ArC_5), 115.0 (ArC_2), 117.7 (ArC_6), 119.9 (ArC_1), remaining peaks buried in baseline noise.

GCMS m/z (relative %): decomposed

(±)-2-tert-butyl-7-ethoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one **(25/26a):**

To a solution of **24a** (0.059 g, 0.23 mmol) in acetone (35 mL) which had stirred at 0°C for 5 minutes was added lead tetraacetate (0.264 g, 0.595 mmol, 2.6 eq.). The resulting mixture was stirred for 2.5 hours at 0°C, filtered through Celite® and ethylene glycol (3 drops) was added. The solution was stirred at room temperature over night, filtered through Celite® and the solvent was evaporated in vacuo. Diethyl ether was used to remove excess ethylene glycol under high vacuum. ^{1}H-NMR of the crude reaction mixture indicated that two diastereomers were produced in a ratio of 76/24. Column chromatography on silica gel (25% Ethyl acetate/Hexanes) afforded as a mixture of diastereomers a clear light yellow oil (92% yield). Characterization was performed on the mixture. Whenever distinguishable, values are given for the one isomer with those of the second isomer listed in square brackets.

IR (neat) cm^{-1}: 1677 (CO)

^{1}H-NMR ($CDCl_3$) δ: 0.94 [0.95] (s, 9H, t-butyl); 1.42 (t, 3H, ethyl CH_3); 1.95 – 2.07 (m, 4H, H_3 and H_4), 3.91 (m, 3H, ethyl CH_2 and H_2), 5.66 (d, 1H, J=2.7Hz, H_6) [5.76 (J=2.7Hz)]; 6.12 (d, 1H, J=9.9Hz, H_9) [6.14 (J=9.9Hz)]; 6.78 (dd, 1H, J=2.7, 9.9Hz, H_{10}) [6.87 (J=2.7, 9.9Hz)]

^{13}C-NMR ($CDCl_3$) δ: 14.5 (ethyl CH_3), 26.1 (t-butyl CH_3), 27.7 (C_3), 33.8 (t-butyl C), 38.4 (C_4), 63.4 (ethyl CH_2), 79.7 (C_5), 88.9 (C_2), 118.0 (C_6), 126.4 (C_9), 149.1 (C_{10}), 150.7 (C_7), 181.4 (CO)

GCMS m/z (relative %): 250 (75), 167 (100), 165 (29), 139 (33), 91 (7)

(±)-2-tert-butyl-7-isopropoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one **(25/26b):**

To a solution of **24b** (0.055 g, 0.21 mmol) in acetone (35 mL) which had stirred at 0°C for 5 minutes was added lead tetraacetate (0.240 g, 0.541 mmol, 2.6 eq.). The resulting mixture was stirred for 2.5 hours at 0°C, filtered through Celite® and ethylene glycol (3 drops) was added. The solution was stirred at room temperature over night, filtered through Celite® and the solvent was evaporated in vacuo. Diethyl ether was used to remove excess ethylene glycol under high vacuum. ^{1}H-NMR of the crude reaction mixture indicated that two diastereomers were produced in a ratio of 71/29. Column chromatography on silica gel (25% Ethyl acetate/Hexanes) afforded as a mixture of diastereomers a clear light yellow oil. Characterization was performed on the mixture. Whenever distinguishable, values are given for the one isomer with those of the second isomer listed in square brackets.

IR (neat) cm^{-1}: 1676 (CO)

^{1}H-NMR ($CDCl_3$) δ: 0.94 [0.95] (s, 9H, t-butyl CH_3), 1.31 [1.34] (d, 6H, i-propyl CH_3), 2.06 (m, 5H, H_2, H_3 and H_4), 3.92 [4.35] (m, 1H, i-propyl CH), 5.67 (d, 1H, J=2.8 Hz, H_6) [5.77 (J=2.7Hz)], 6.11 (d, 1H, J=10.0 Hz, H_9) [6.13 (J=10.0 Hz)], 6.76 (dd, 1H, J=2.7, 10.0 Hz, H_{10}) [6.84 (J=2.7, 10.0 Hz)]

^{13}C-NMR ($CDCl_3$) δ: 21.95 (i-propyl CH_3), 26.26 (t-butyl CH_3), 34.00 (t-butyl C), 38.59 (C_4), 79.89 (C_5), 89.14 (C_2), 119.75 (C_6), 126.70 (C_9), 147.90 (C_{10}), 150.58 (C_7), 182.19 (CO)

GCMS m/z (relative %): 264(100), 205 (11), 165 (58), 123(51)

(±)-2-tert-Butyl-7-methylcyclohexyloxy-1-oxaspiro[4,5]deca-6,9-diene-8-one **(25/26c):**

To a solution of **24c** (0.037 g, 0.12 mmol) in acetone (35 mL) which had stirred at 0°C for 5 minutes was added lead tetraacetate (0.138 g, 0.311 mmol, 2.6 eq.). The resulting mixture was stirred for 2.5 hours, filtered through Celite® and ethylene glycol (3 drops) was added. The solution was stirred at room temperature over night, filtered through Celite® and the solvent was evaporated in vacuo. Diethyl ether was used to remove excess ethylene glycol under high vacuum. ^{1}H-NMR of the crude reaction mixture indicated that two diastereomers were produced in a ratio of 65/35. Column chromatography on silica gel (25% Ethyl acetate/Hexanes) afforded as a mixture of diastereomers a clear light yellow oil. Characterization was performed on the mixture. Whenever distinguishable, values are given for the one isomer with those of the second isomer listed in square brackets.

IR (neat) cm^{-1}: 1678 (CO)

^{1}H-NMR ($CDCl_3$) δ: 0.95 [0.96] (s, 9H, t-Bu CH_3); 1.26 (m, 4H, cyclohexyl), 1.84 (m, 4H, cyclohexyl)[1.88]; 2.08 (m, 3H, cyclohexyl), 3.53 (d, 2H, OCH_2), 3.93 (m, 1H, H_2), 5.62 (d,

1H, J=2.6Hz, H_6) [5.74 (J=2.7Hz)]; 6.12 (d, 1H, J=9.9Hz, H_9) [6.14 (J=9.9Hz)]; 6.77 (dd, 1H, J=2.7, 10.0Hz, H_{10}) [6.87 (J=2.7, 9.9Hz)]

^{13}C-NMR ($CDCl_3$) δ: 25.9 (t-Bu CH_3), 26.1 ($C_{3'}$, $C_{5'}$), 26.7 ($C_{4'}$), 27.5 [27.7](C_3), 30.2 ($C_{2'}$,$C_{6'}$), 33.8 (t-butyl C), 37.2 ($C_{1'}$), 38.1 [38.4] (C_4), 73.3 (C_5), 79.7 (OCH_2), 88.7 (C_2), 117.8 (C_6), 126.5 (C_9), 149.5 (C_{10}), 150.4 (C_7), 181.3 (CO)

GCMS m/z (relative %): 316 (100), 204 (12), 123 (7)

(±)-2-tert-butyl-7-(2,6-dichlorobenzyloxy)-1-oxaspiro[4,5]deca-6,9-diene-8-one **(25/26d):** To a solution of **24d** (0.051 g, 0.13 mmol) in acetone (35 mL) which had stirred at 0°C for 5 minutes was added lead tetraacetate (0.151 g, 0.341 mmol, 2.6 eq.). The resulting mixture was stirred for 2.5 hours at 0°C, filtered through Celite® and ethylene glycol (3 drops) was added. The solution was stirred at room temperature over night, filtered through Celite® and the solvent was evaporated in vacuo. Diethyl ether was used to remove excess ethylene glycol under high vacuum. ^{1}H-NMR of the crude reaction mixture indicated that two diastereomers were produced in a ratio of 50/50. Column chromatography on silica gel (20% Ethyl acetate/Hexanes) afforded as a mixture of diastereomers a clear light yellow oil. Characterization was performed on the mixture. Whenever distinguishable, values are given for the one isomer with those of the second isomer listed in square brackets.

IR (neat) cm^{-1}: 1677 (CO)

^{1}H-NMR ($CDCl_3$) δ: 0.96 [0.97] (s, 9H, t-Bu), 2.05 (m, 4H, H_3 and H_4), 3.97 (m, 1H, H_2), 5.08 (s, 2H, OCH_2), 5.88 (d, 1H, J=2.7Hz, H_6) [5.98 (J=2.7Hz)]; 6.13 (d, 1H, J=10.0Hz, H_9) [6.14 (J=9.9Hz); 6.79 (dd, 1H, J=2.7, 10.0Hz, H_{10}) [6.87 (J=2.7, 9.9Hz)], 7.30 (m, 3H, DiClBz)

^{13}C-NMR ($CDCl_3$) δ: 26.1 (t-Bu CH_3), 27.6 [27.7] (C_3), 33.8 (t-Bu C), 38.1 [38.4] (C_4), 65.0 [65.1] (OCH_2), 79.6 [79.7] (C_5), 88.9 [89.0] (C_2), 119.5 [119.7] (C_6), 126.5 (C_9), 128.6 ($DiClBzC_3$, $DiClBzC_5$), 130.8 ($DiClBzC_4$), 131.4 ($DiClBzC_2$, $DiClBzC_6$), 137.4 ($DiClBzC_1$), 149.1 (C_{10}), 150.4 (C_7), 180.7 (CO)

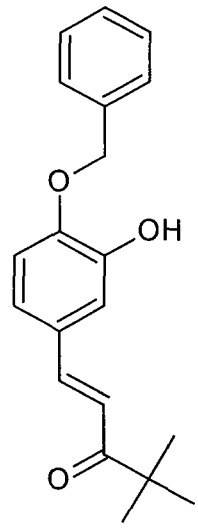
GCMS m/z (relative %): 381(100), 205 (66)

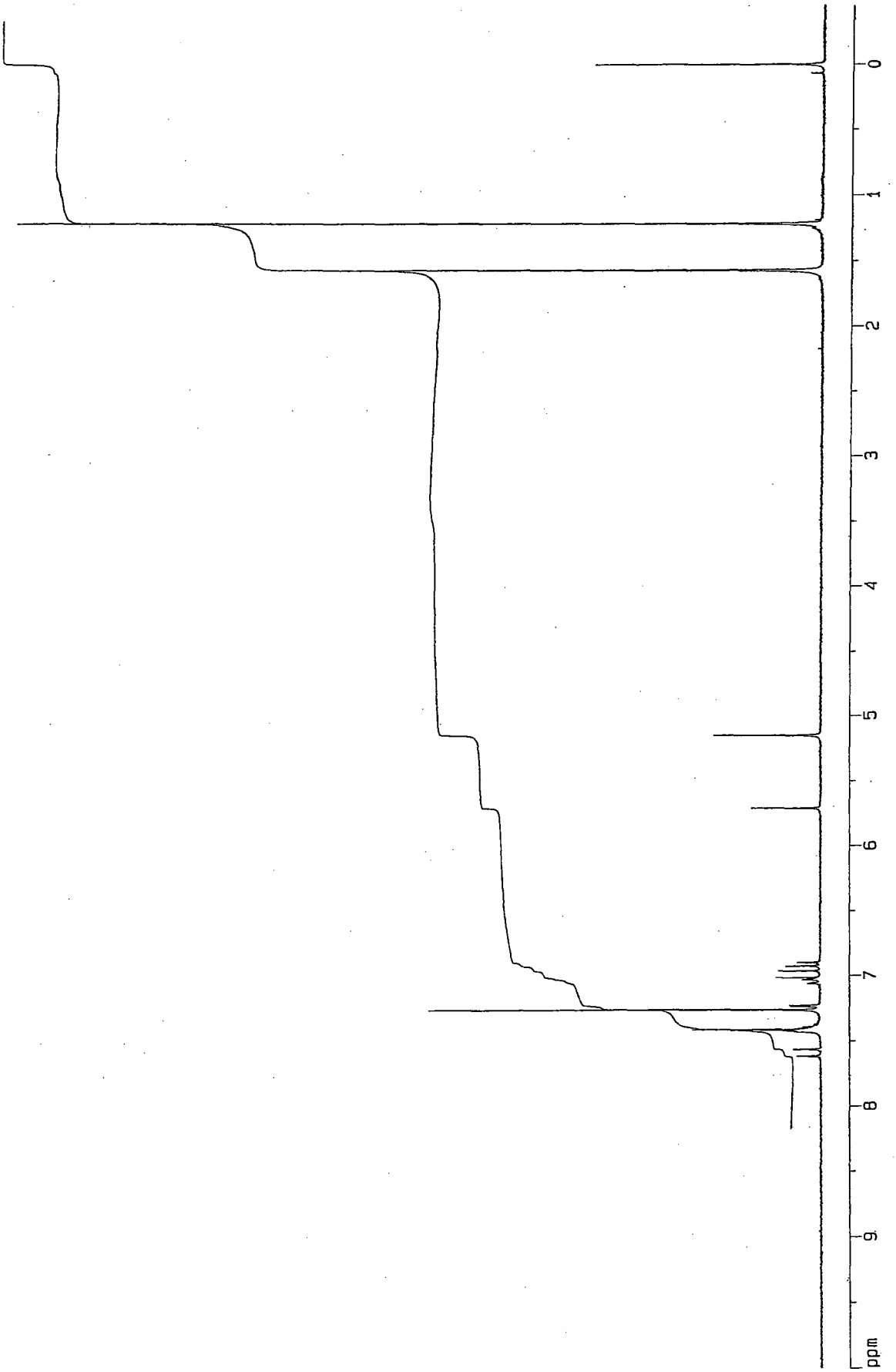
(±)-2-tert-Butyl-7-(t-butyldimethylsilyloxy)-1-oxaspiro[4,5]deca-6,9-diene-8-one **(25/26e):** To a solution of **24e** (0.032g, 0.095 mmol) in acetone (35 mL) which had stirred at 0°C for 5 minutes was added lead tetraacetate (0.105g, 0.237 mmol, 2.5 eq.). The resulting mixture was stirred for 2.5 hours at 0°C, filtered through Celite® and ethylene glycol (3 drops) was added. The solution was stirred at room temperature over night, filtered through Celite® and the solvent was evaporated in vacuo. Diethyl ether was used to remove excess ethylene glycol under high vacuum. Determination of the ratio of diastereomers from the ^{1}H-NMR of crude product was not possible as the peaks of interest were barely discernable within the noise of the spectrum. Chromatography (25% EtOAc/1% Et_3N/hexane) of the crude material did not yield any product. It appeared to decompose on the column.

Appendix 1

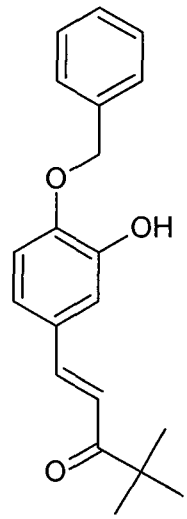
NMR Spectra of Compounds in Numerical Order

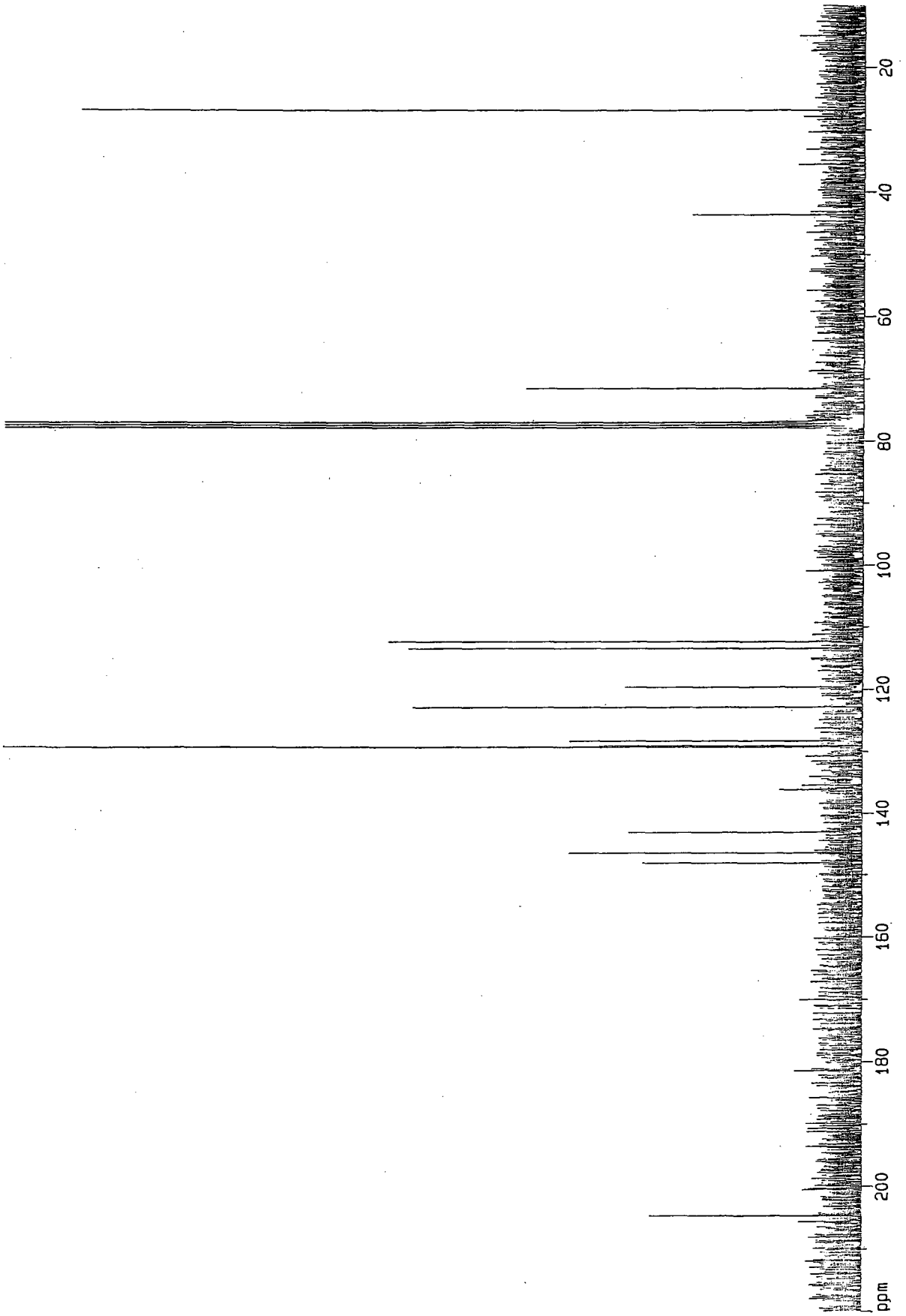
^{1}H-NMR Spectrum of
(1E)-1-[4-(benzyloxy)-3-hydroxyphenyl]-4,4-dimethylpent-1-en-3-one (**22**)



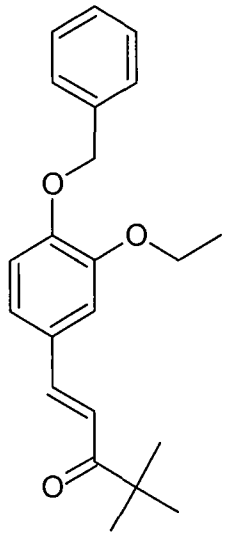

0
1
2
3
4
5
6
7
8
9
ppm

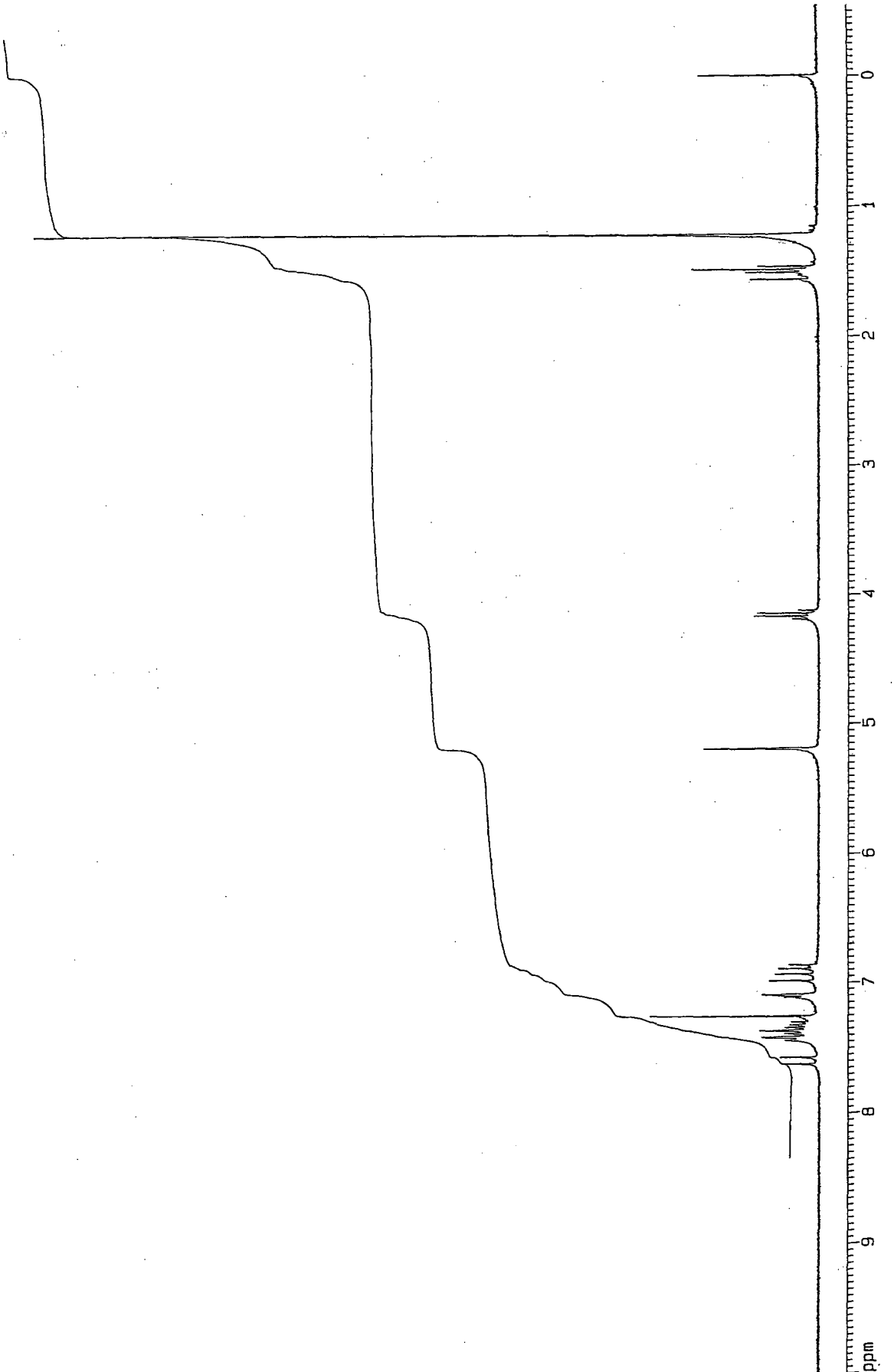
^{13}C-NMR Spectrum of
(1E)-1-[4-(benzyloxy)-3-hydroxyphenyl]-4,4-dimethylpent-1-en-3-one (**22**)



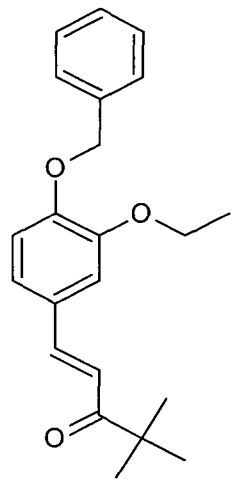

20
40
60
80
100
120
140
160
180
200
ppm

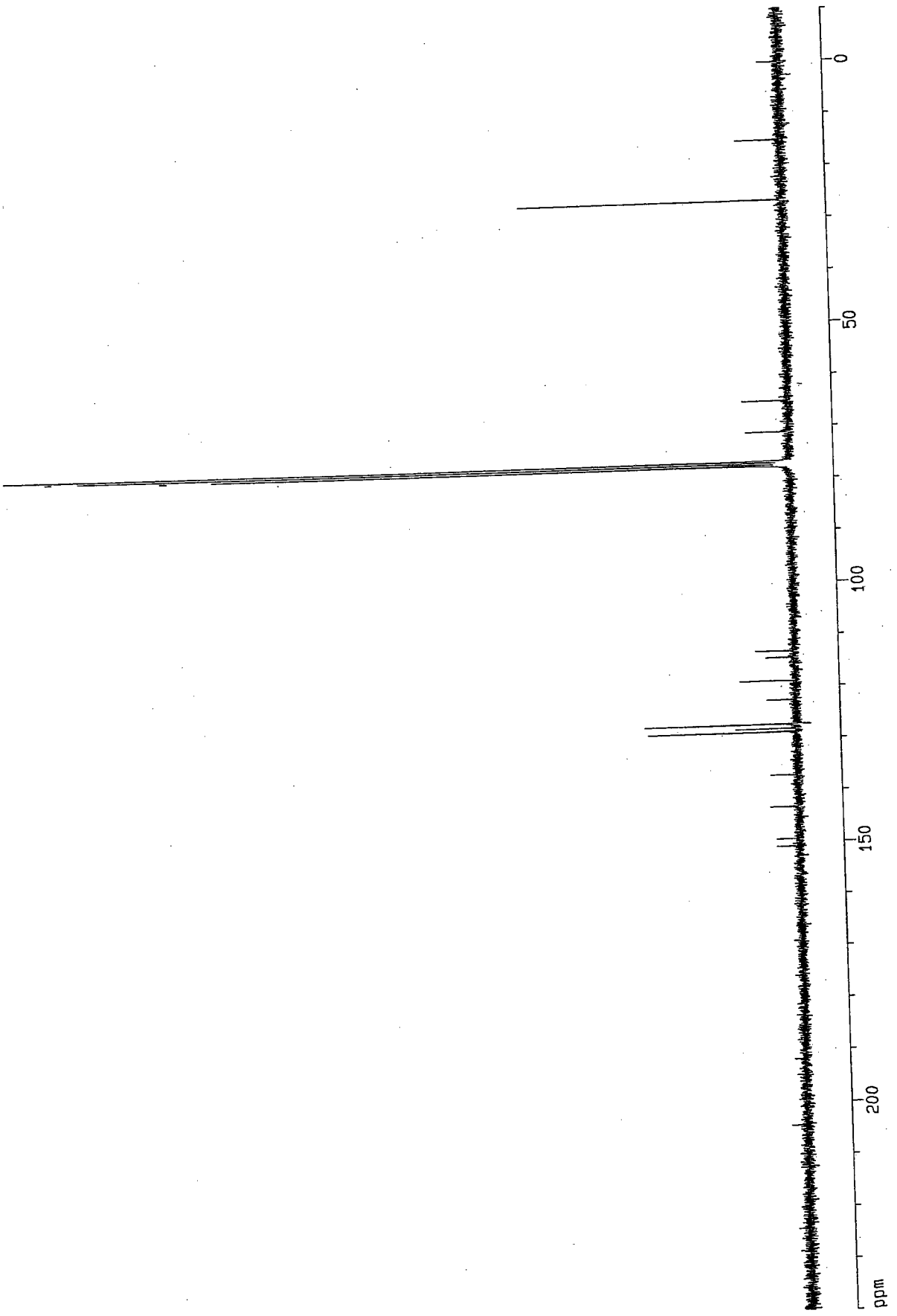
^{1}H-NMR Spectrum of
1-(4-benzyloxy-3-ethoxyphenyl)-4,4-dimethyl-1-penten-3-one (**23a**)



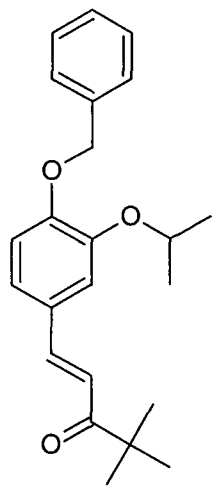

0
1
2
3
4
5
6
7
8
9
ppm

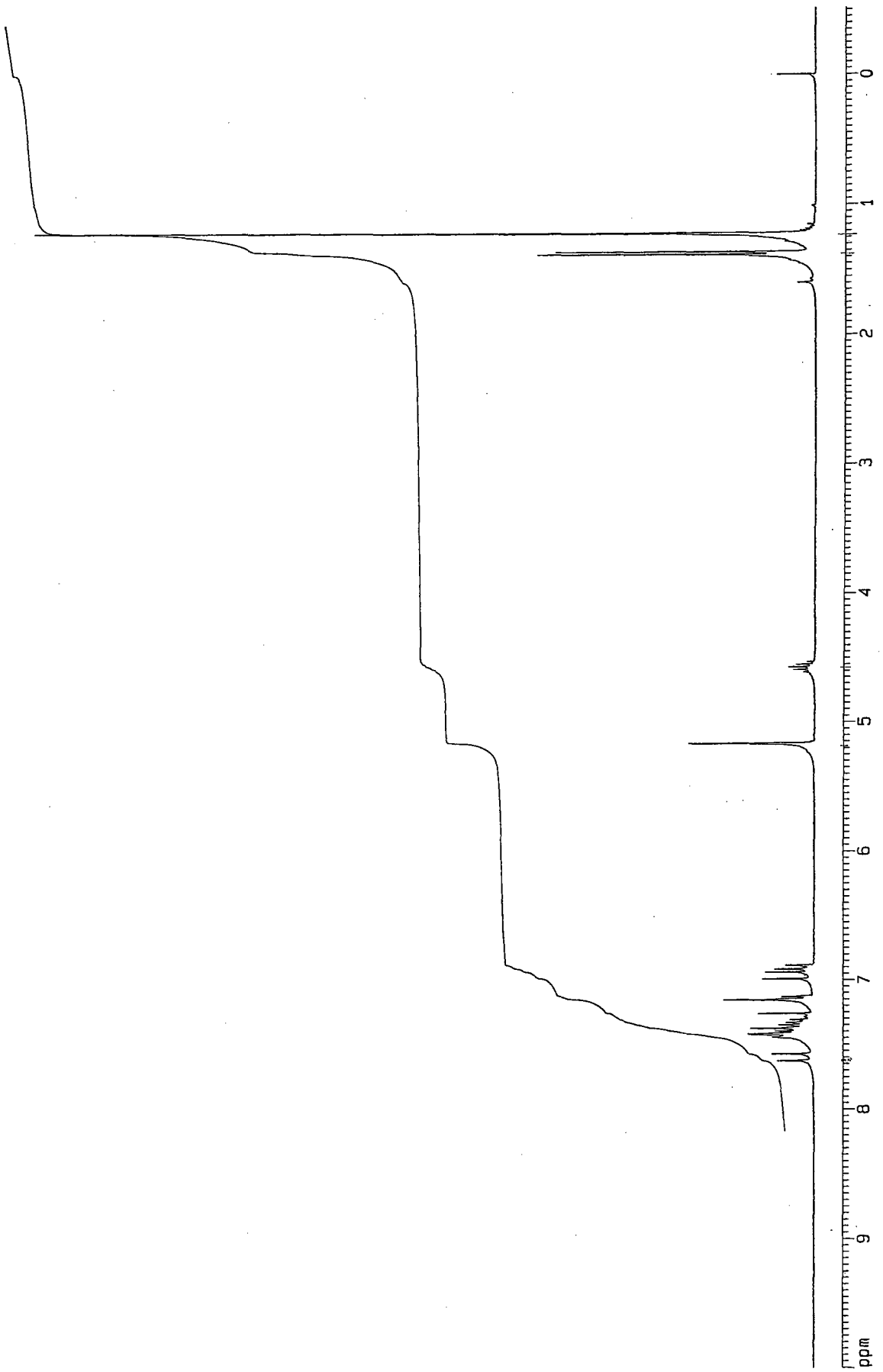
^{13}C-NMR Spectrum of
1-(4-benzyloxy-3-ethoxyphenyl)-4,4-dimethyl-1-penten-3-one (**23a**)



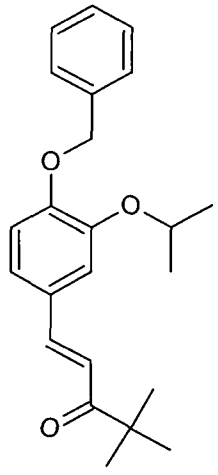

0
50
100
150
200
ppm

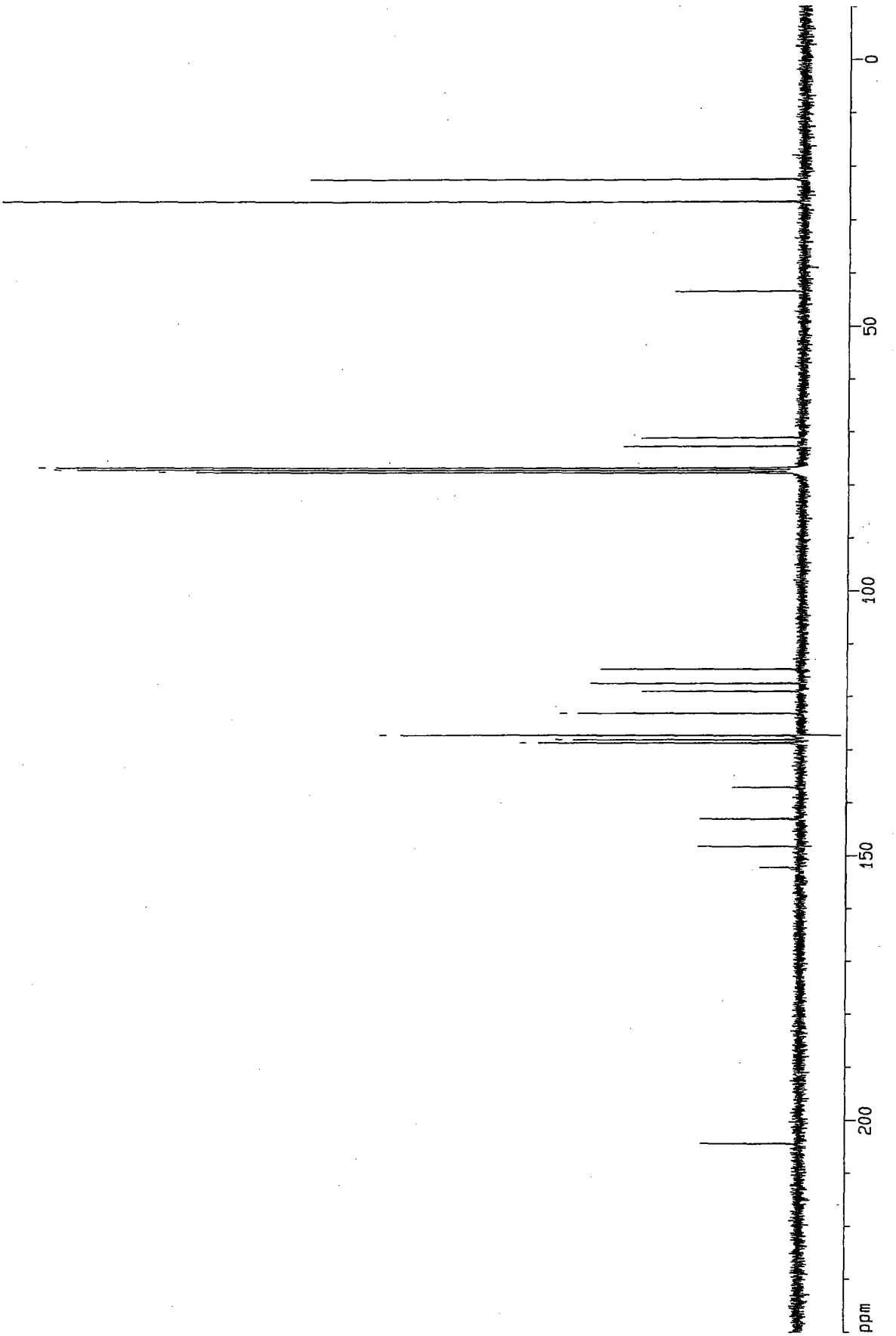
^{1}H-NMR Spectrum of
1-(4-benzyloxy-3-isopropoxyphenyl)-4,4-dimethyl-1-penten-3-one (**23b**)



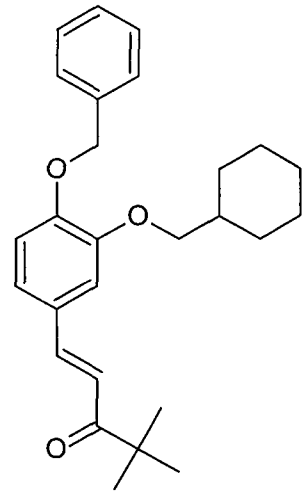

0
1
2
3
4
5
6
7
8
9
ppm

^{13}C-NMR Spectrum of
1-(4-benzyloxy-3-isopropoxyphenyl)-4,4-dimethyl-1-penten-3-one (**23b**)



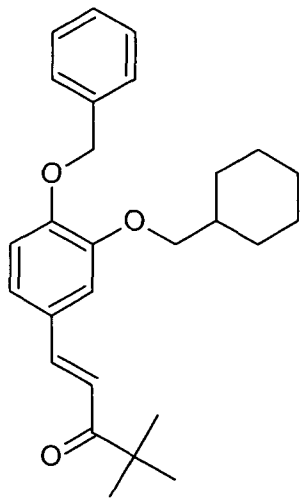

0
50
100
150
200
ppm

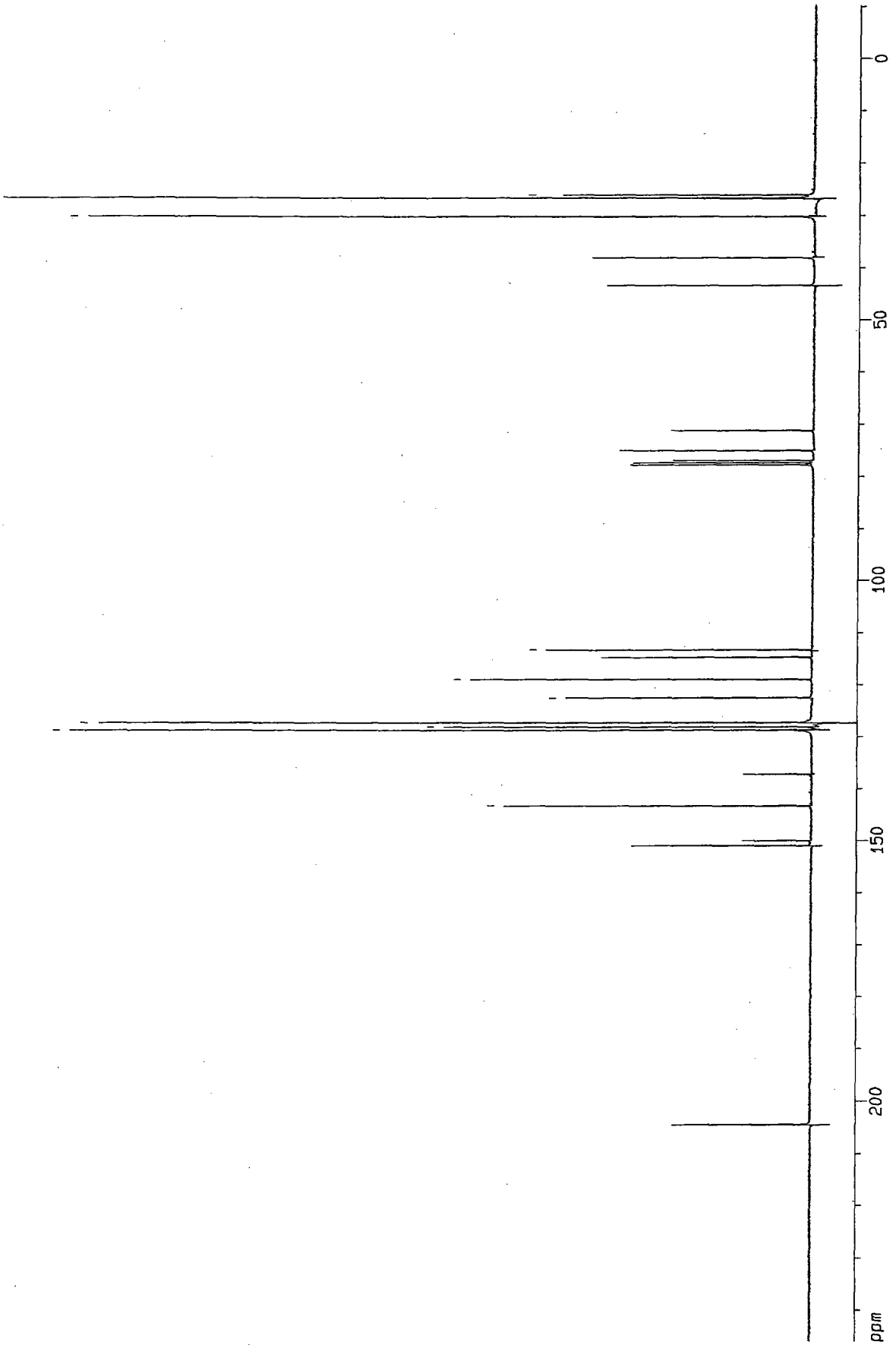
^{1}H-NMR Spectrum of
1-(4-benzyloxy-3-methylcyclohexyloxyphenyl)-4,4-dimethyl-1-penten-3-one (**23c**)



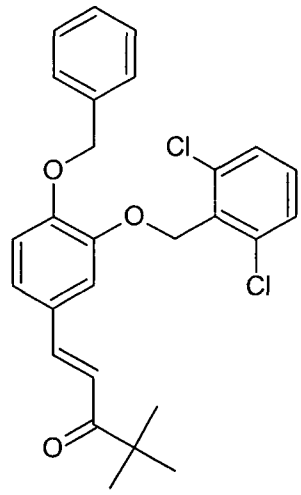

0
1
2
3
4
5
6
7
8
9
ppm

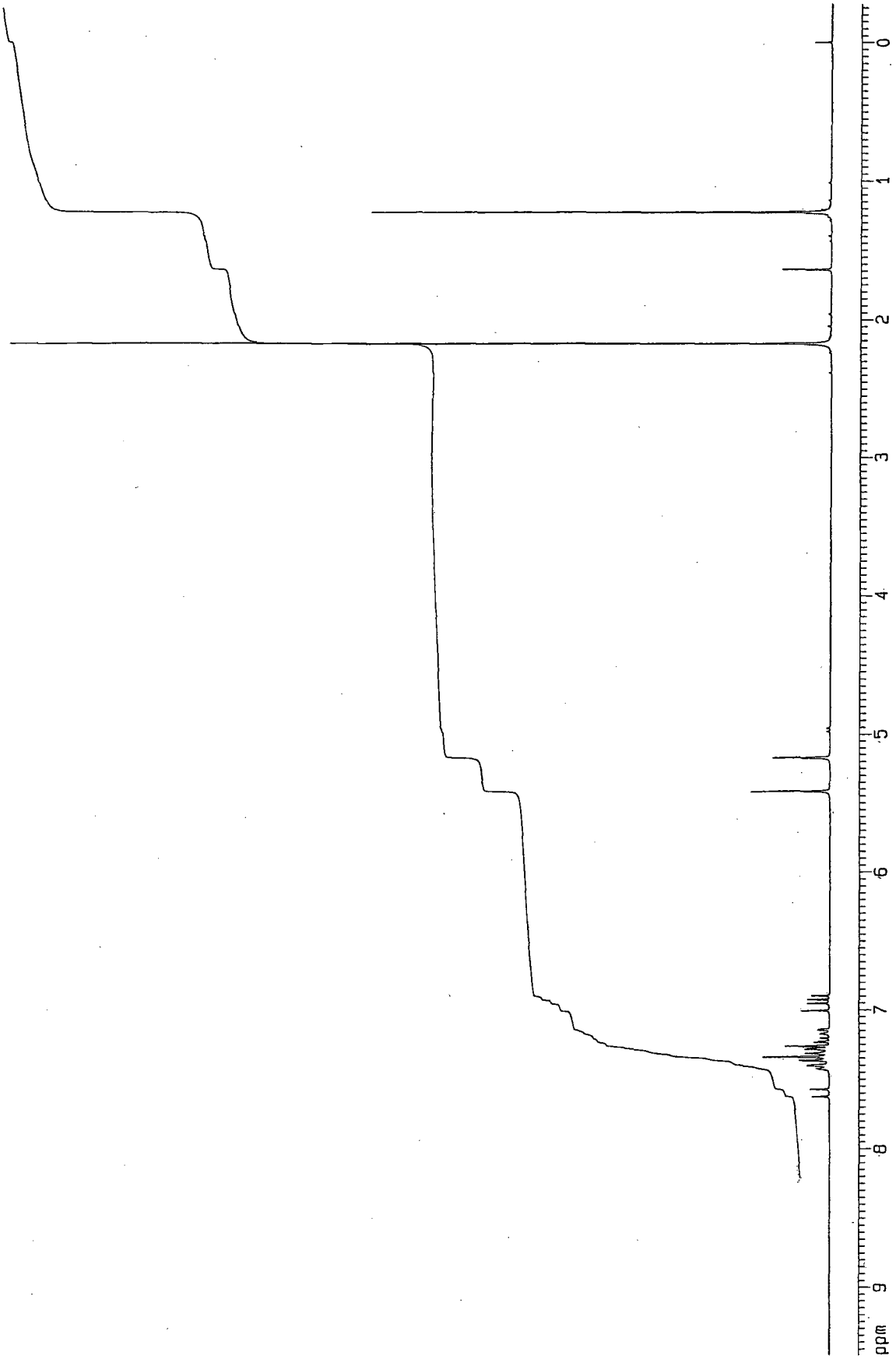
^{13}C-NMR Spectrum of
1-(4-benzyloxy-3-methylcyclohexyloxyphenyl)-4,4-dimethyl-1-penten-3-one (**23c**)



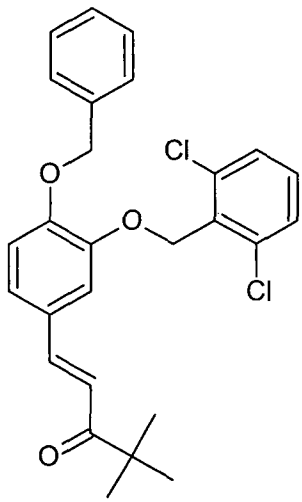

0
50
100
150
200
ppm

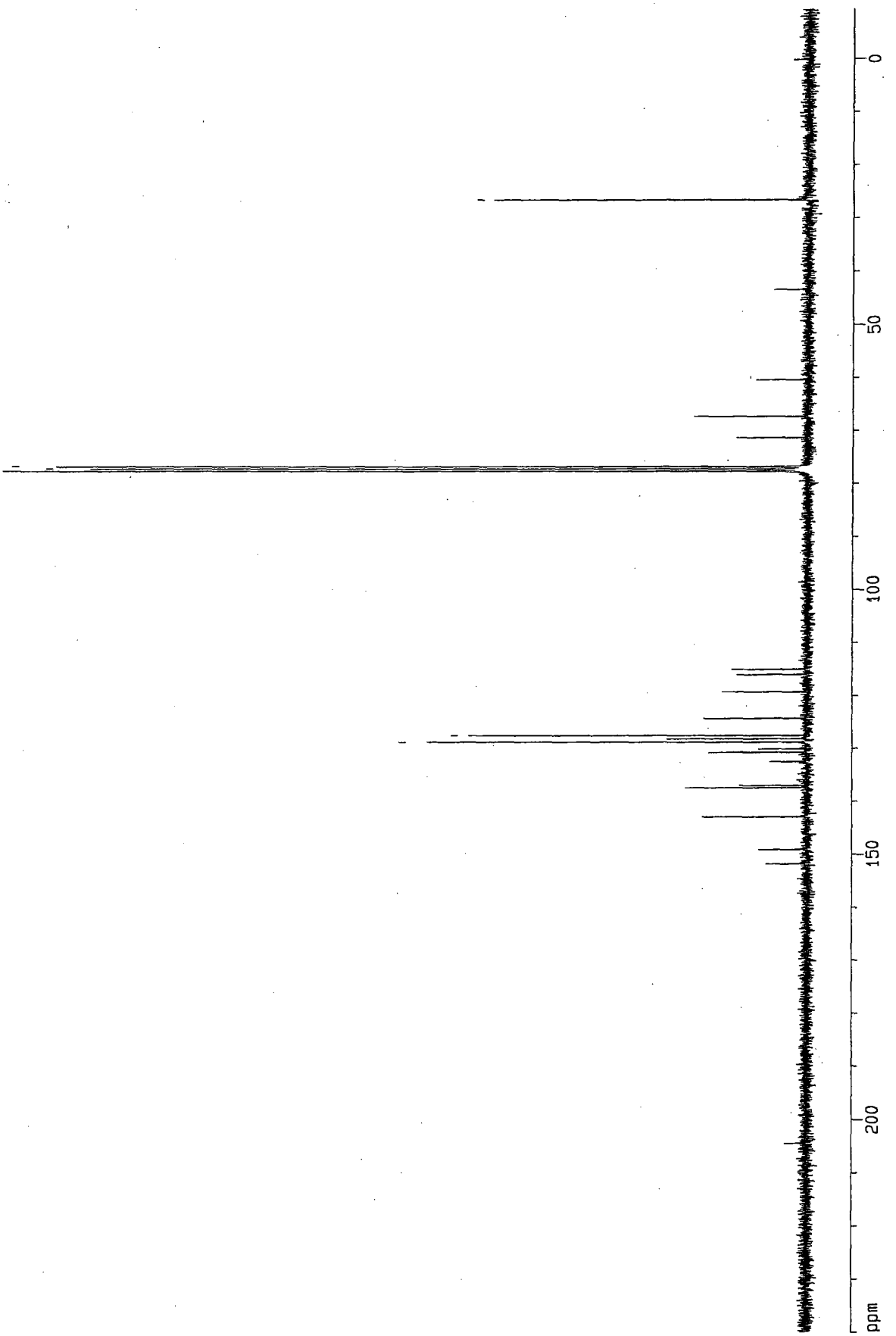
^{1}H-NMR Spectrum of
1-(4-benzyloxy-3-(2,6-dichlorobenzyloxy)-4,4-dimethyl-1-penten-3-one (**23d**)



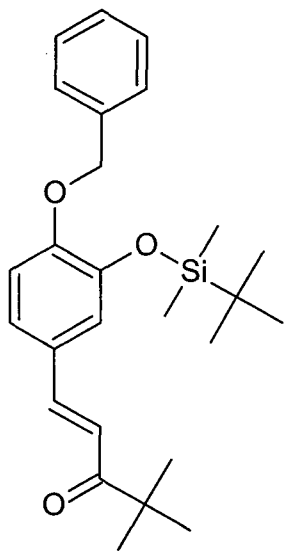

ppm
9
8
7
6
5
4
3
2
1
0

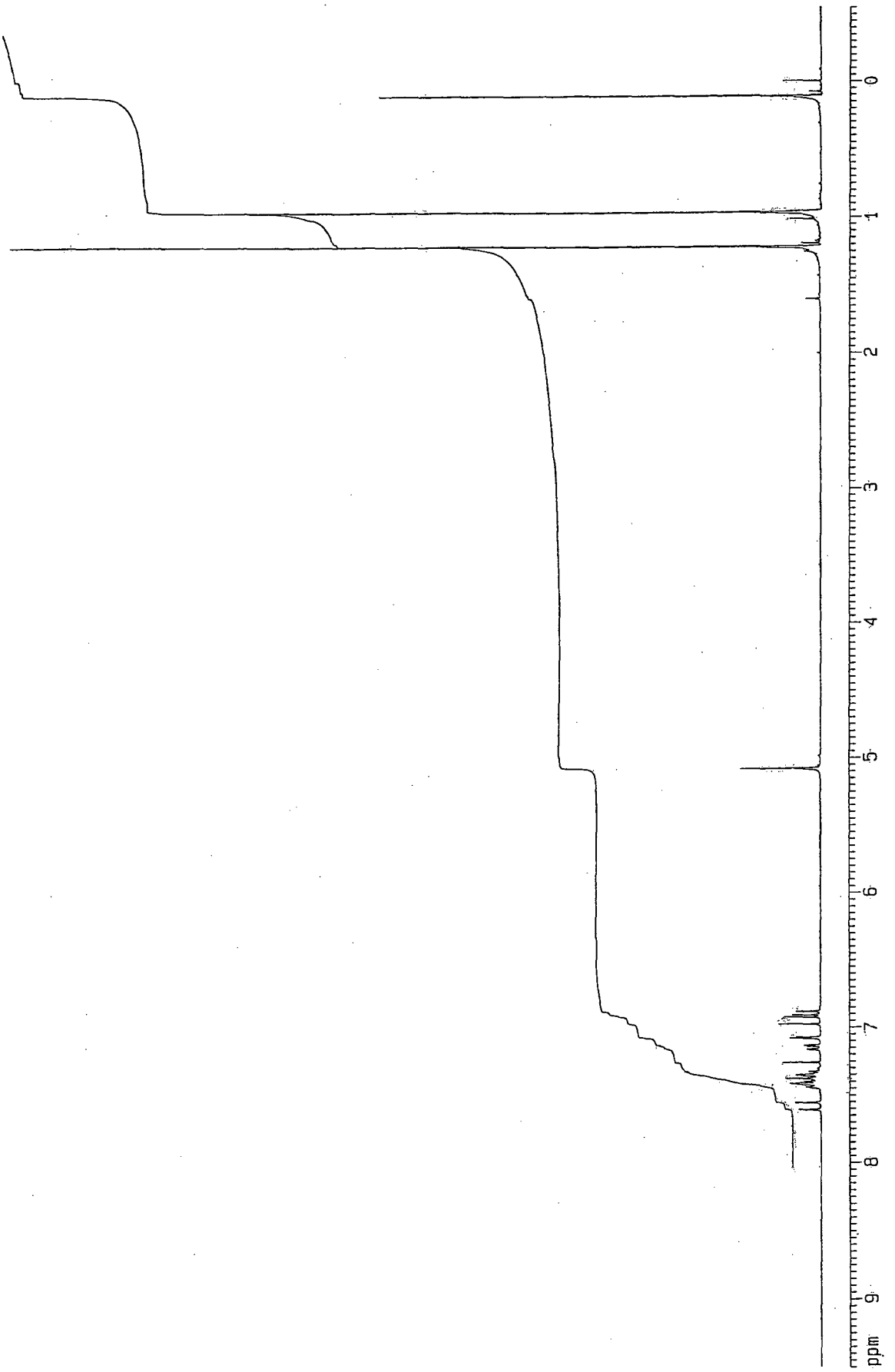
^{13}C-NMR Spectrum of
1-(4-benzyloxy-3-(2,6-dichlorobenzyloxy)-4,4-dimethyl-1-penten-3-one (**23d**)



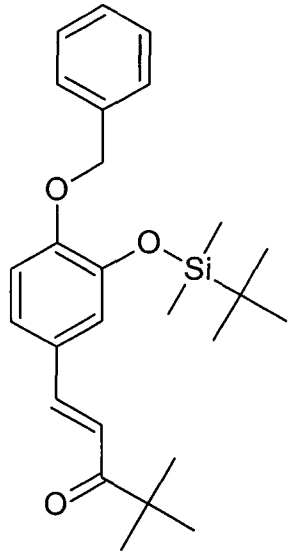

0
50
100
150
200
ppm

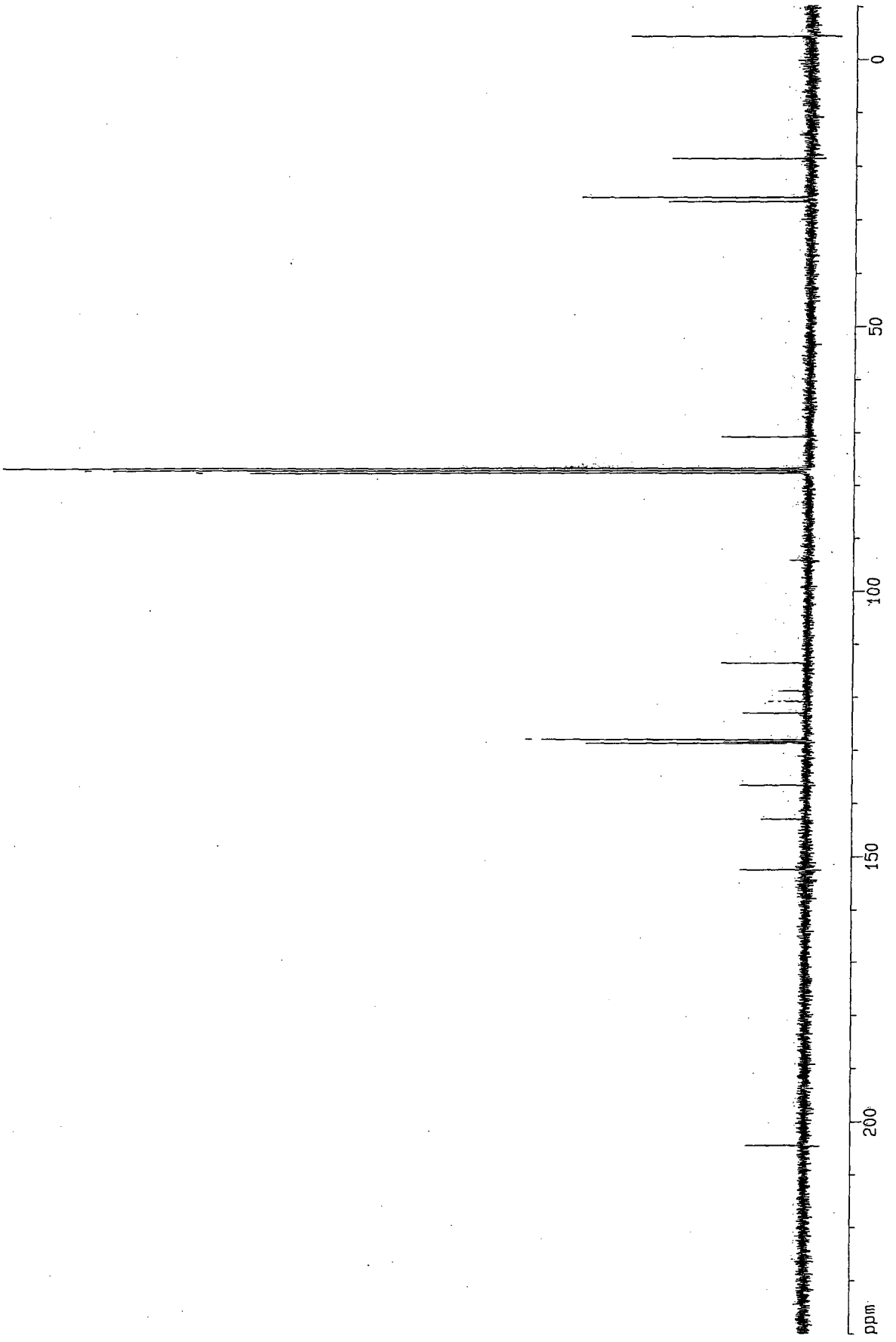
^{1}H-NMR Spectrum of
1-(4-benzyloxy-3-t-butyldimethylsilyloxy)-4,4-dimethyl-1-penten-3-one (**23e**)



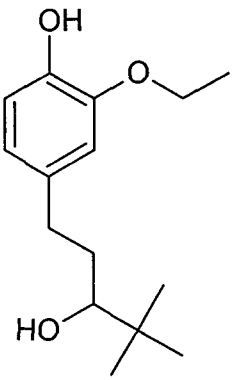

0
1
2
3
4
5
6
7
8
9
ppm

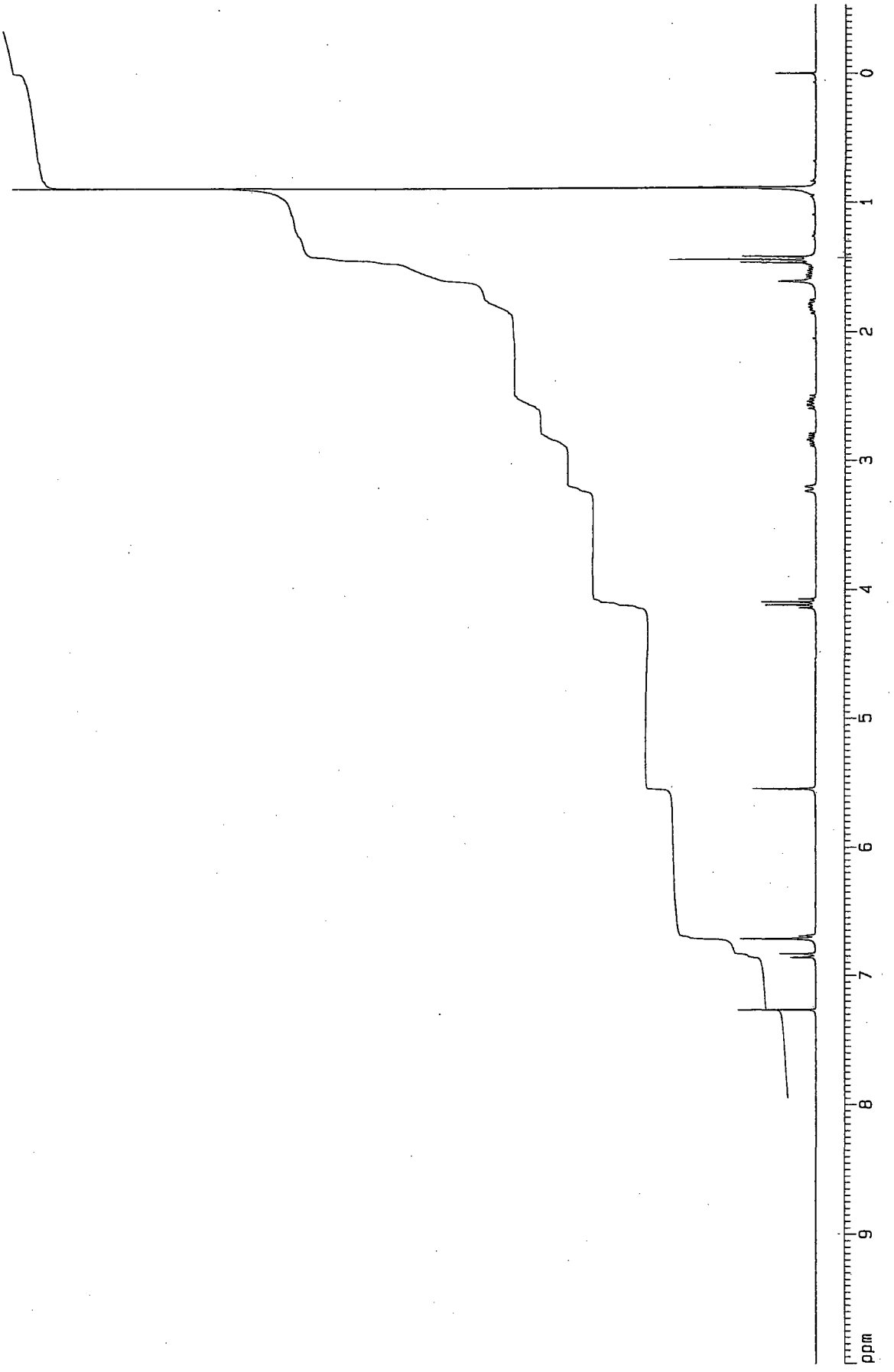
^{13}C-NMR Spectrum of
1-(4-benzyloxy-3-t-butyldimethylsilyloxy)-4,4-dimethyl-1-penten-3-one (**23e**)



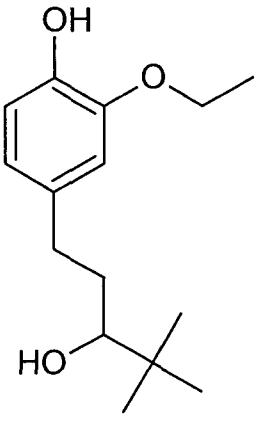

0
50
100
150
200
ppm

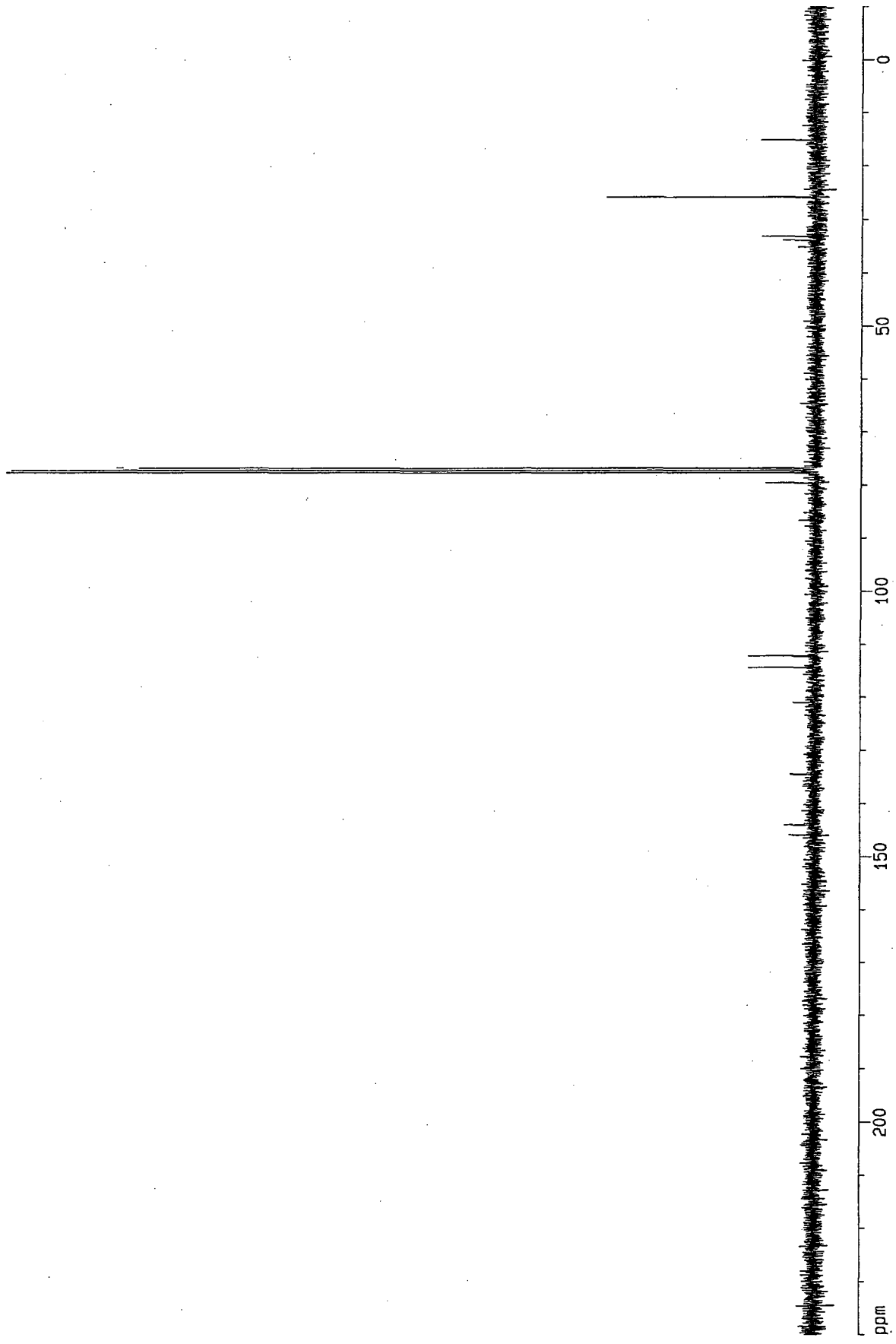
^{1}H-NMR Spectrum of
(±)-1-(3-ethoxy-4-hydroxyphenyl)-4,4-dimethyl-3-pentanol (**24a**)



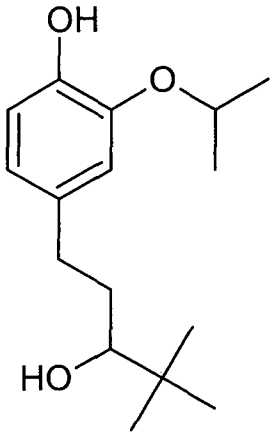

0
1
2
3
4
5
6
7
8
9
ppm

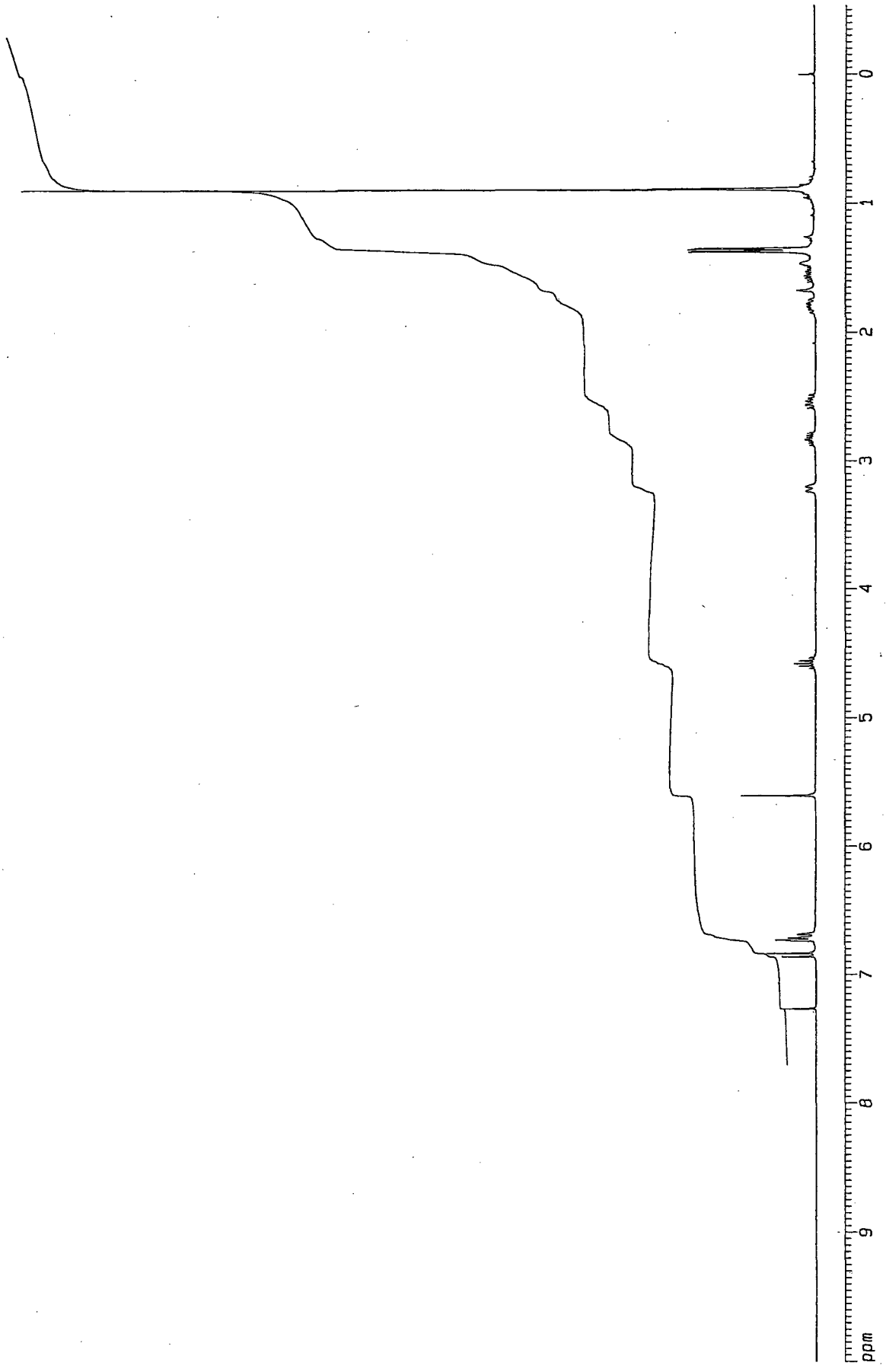
^{13}C-NMR Spectrum of
(±)-1-(3-ethoxy-4-hydroxyphenyl)-4,4-dimethyl-3-pentanol (**24a**)



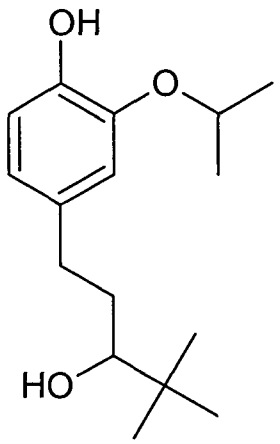

0
50
100
150
200
ppm

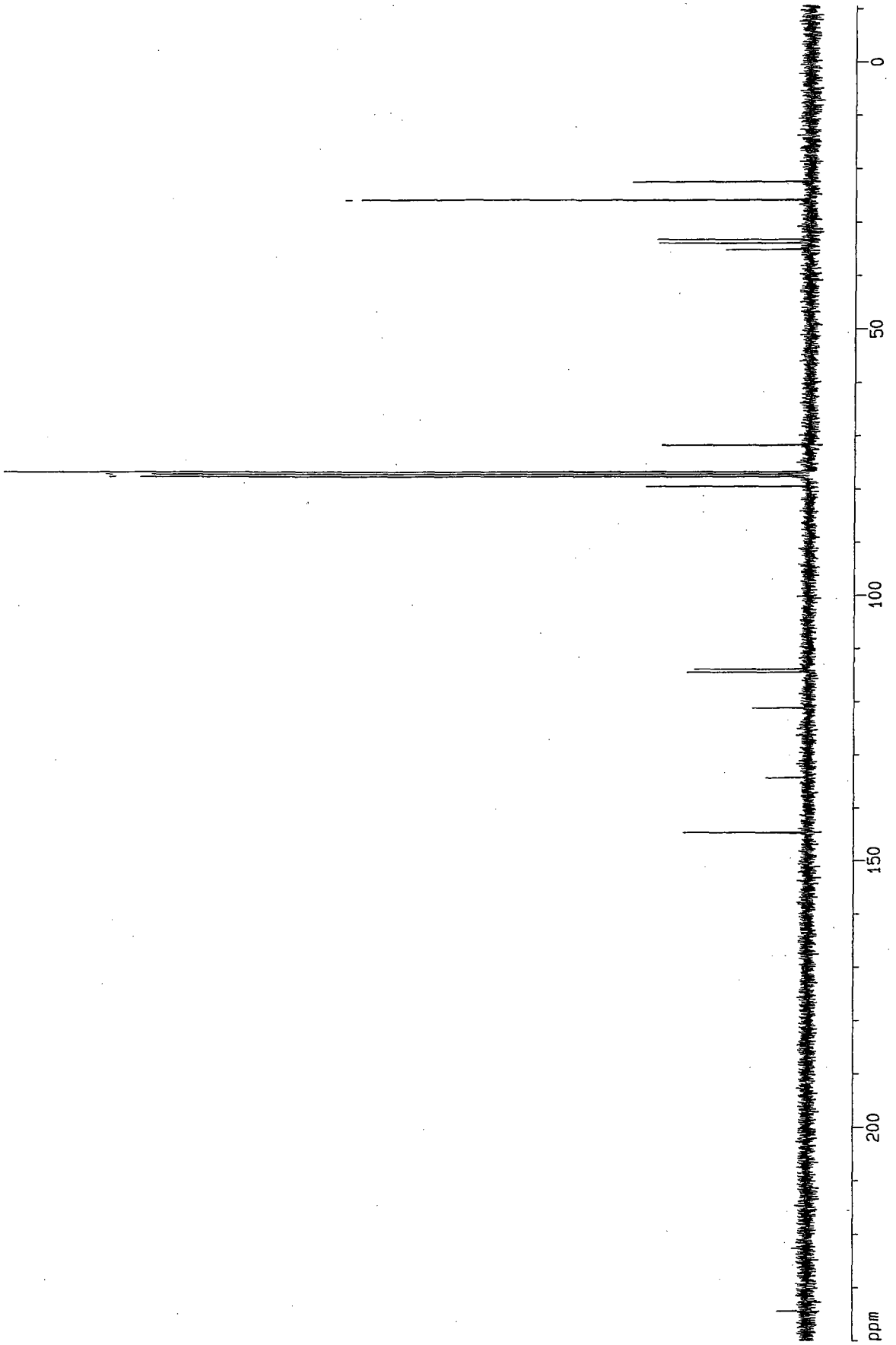
^{1}H-NMR Spectrum of
(±)1-(4-hydroxy-3-isopropylphenyl)-4,4-dimethyl-3-pentanol (**24b**)



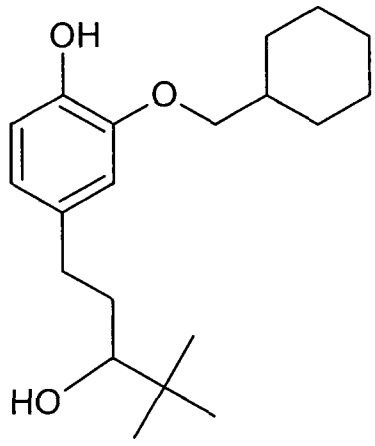

0
1
2
3
4
5
6
7
8
9
ppm

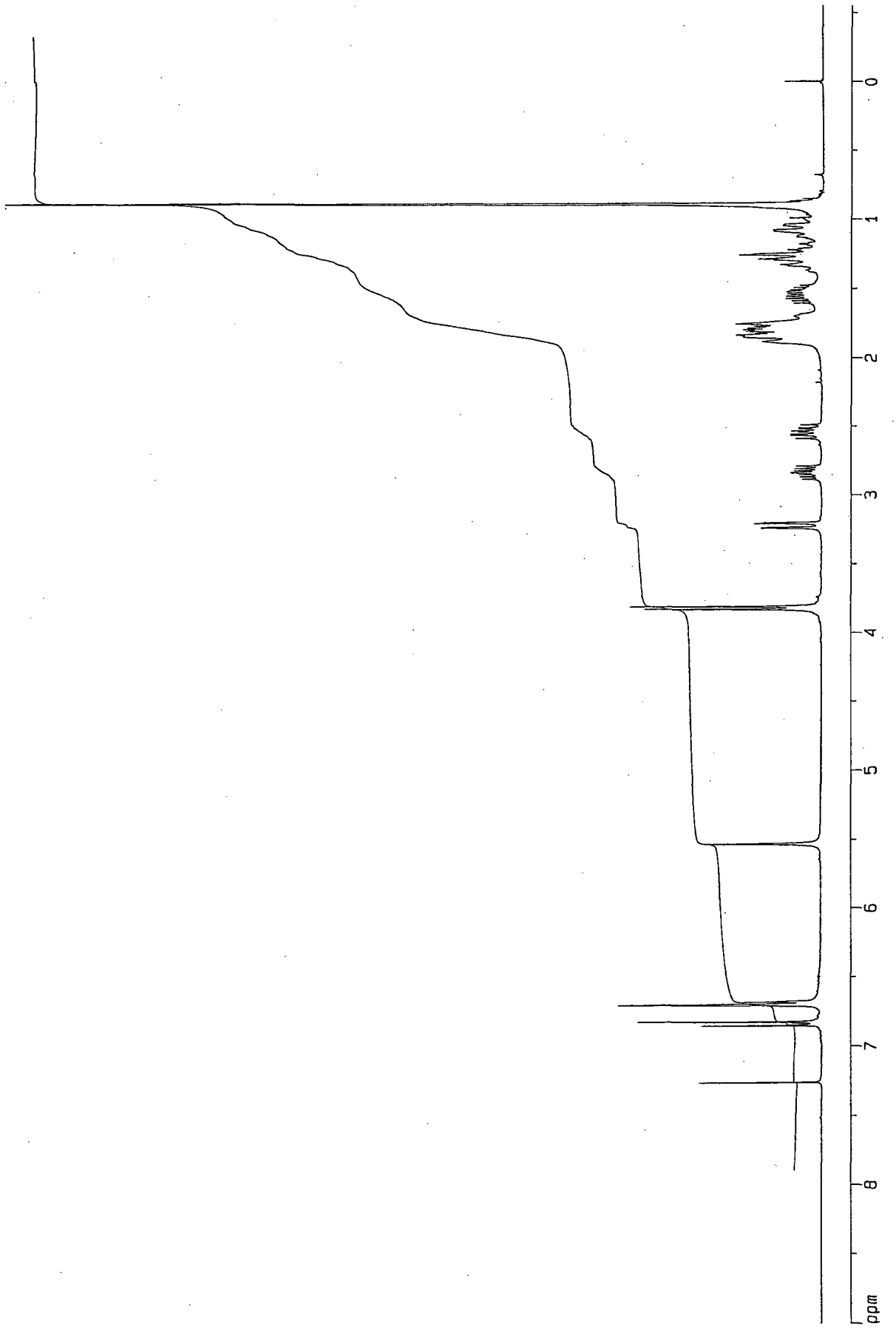
^{13}C-NMR Spectrum of
(±)1-(4-hydroxy-3-isopropylphenyl)-4,4-dimethyl-3-pentanol (**24b**)



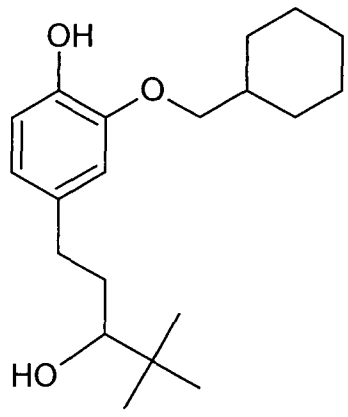

0
50
100
150
200
ppm

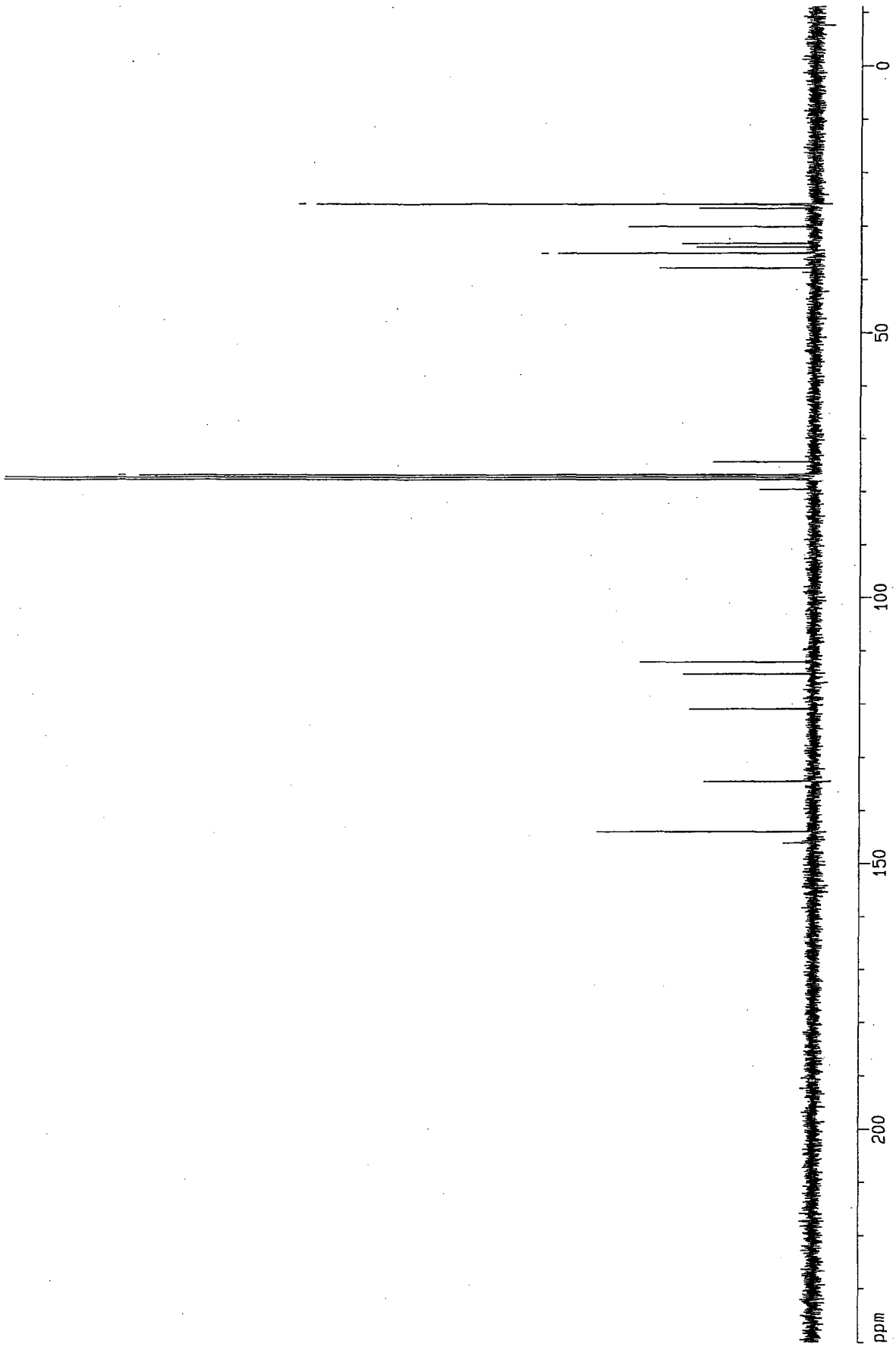
^{1}H-NMR Spectrum of
(±)-1-(4-hydroxy-3-methylcyclohexyloxy)-4,4-dimethyl-3-pentanol (**24c**)



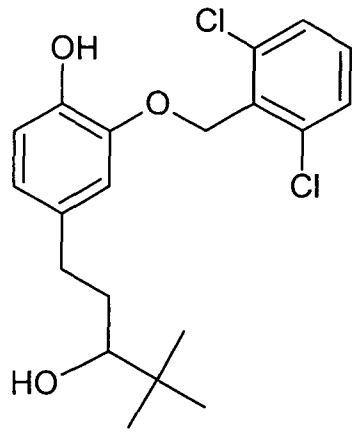

0
1
2
3
4
5
6
7
8
ppm

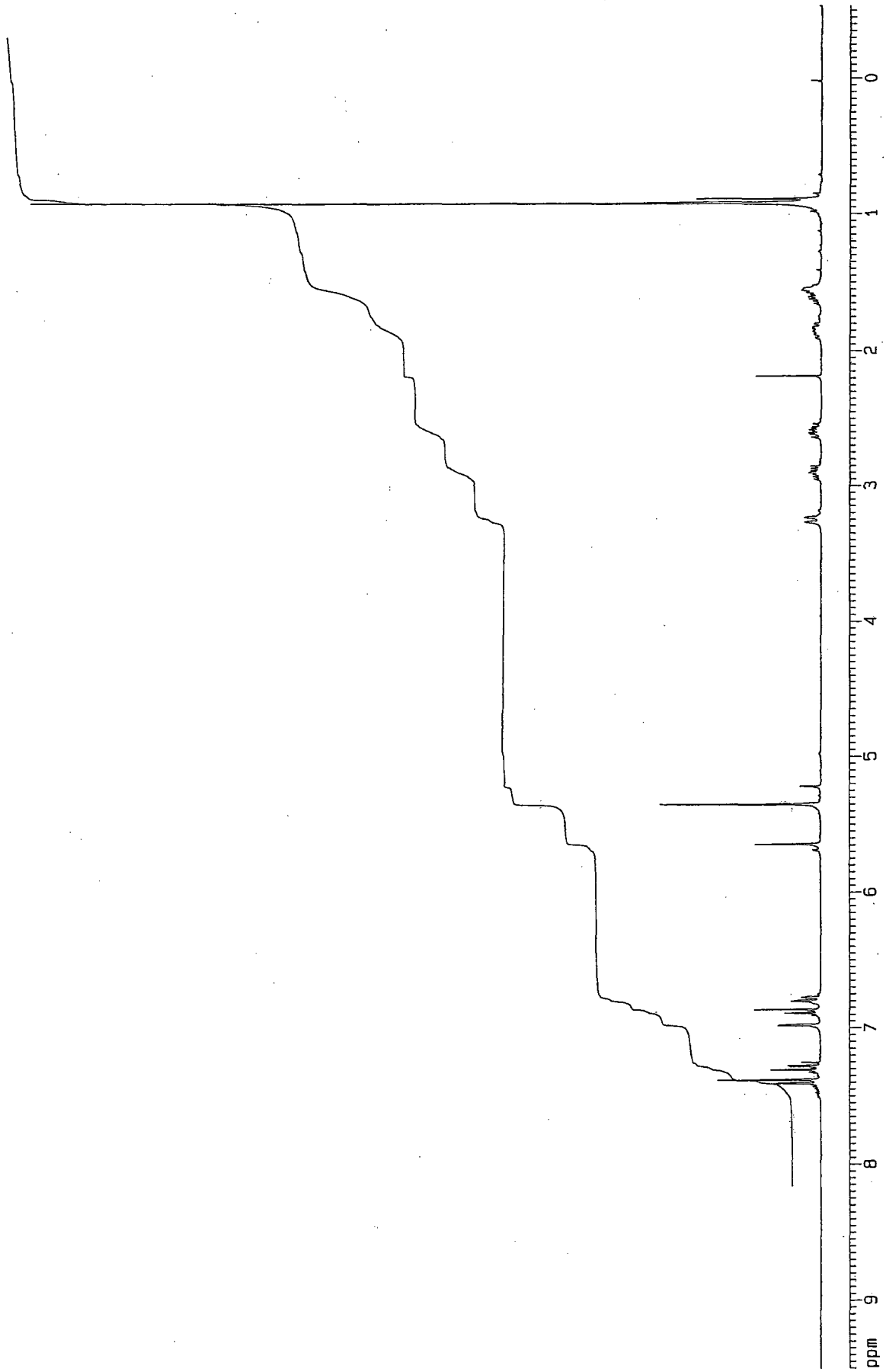
^{13}C-NMR Spectrum of
(±)-1-(4-hydroxy-3-methylcyclohexyloxy)-4,4-dimethyl-3-pentanol (**24c**)



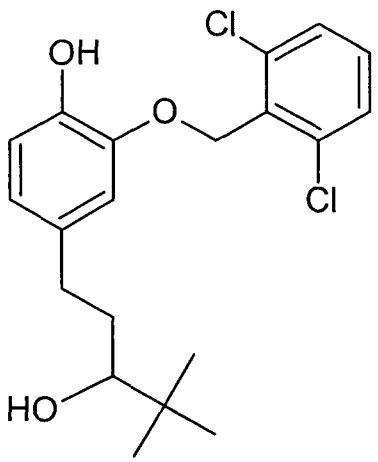

0
50
100
150
200
ppm

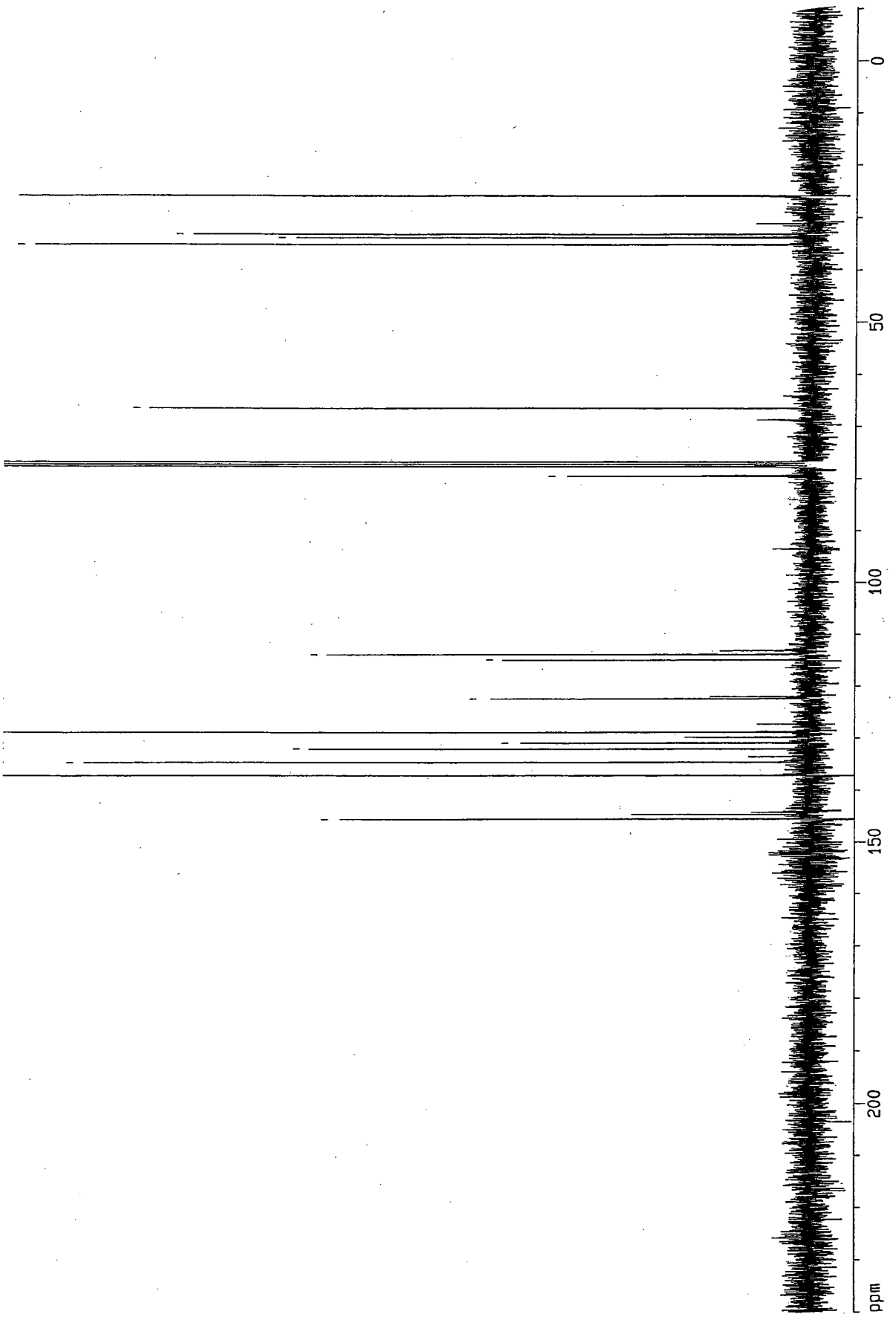
^{1}H-NMR Spectrum of
(±)-1-(3-(2,6-dichlorobenzyloxy)-4-hydroxy)-4,4-dimethyl-3-pentanol (**24d**)



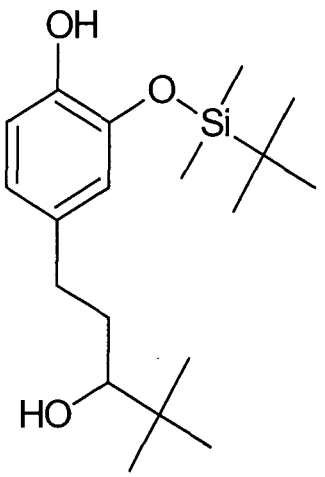

0
1
2
3
4
5
6
7
8
9
ppm

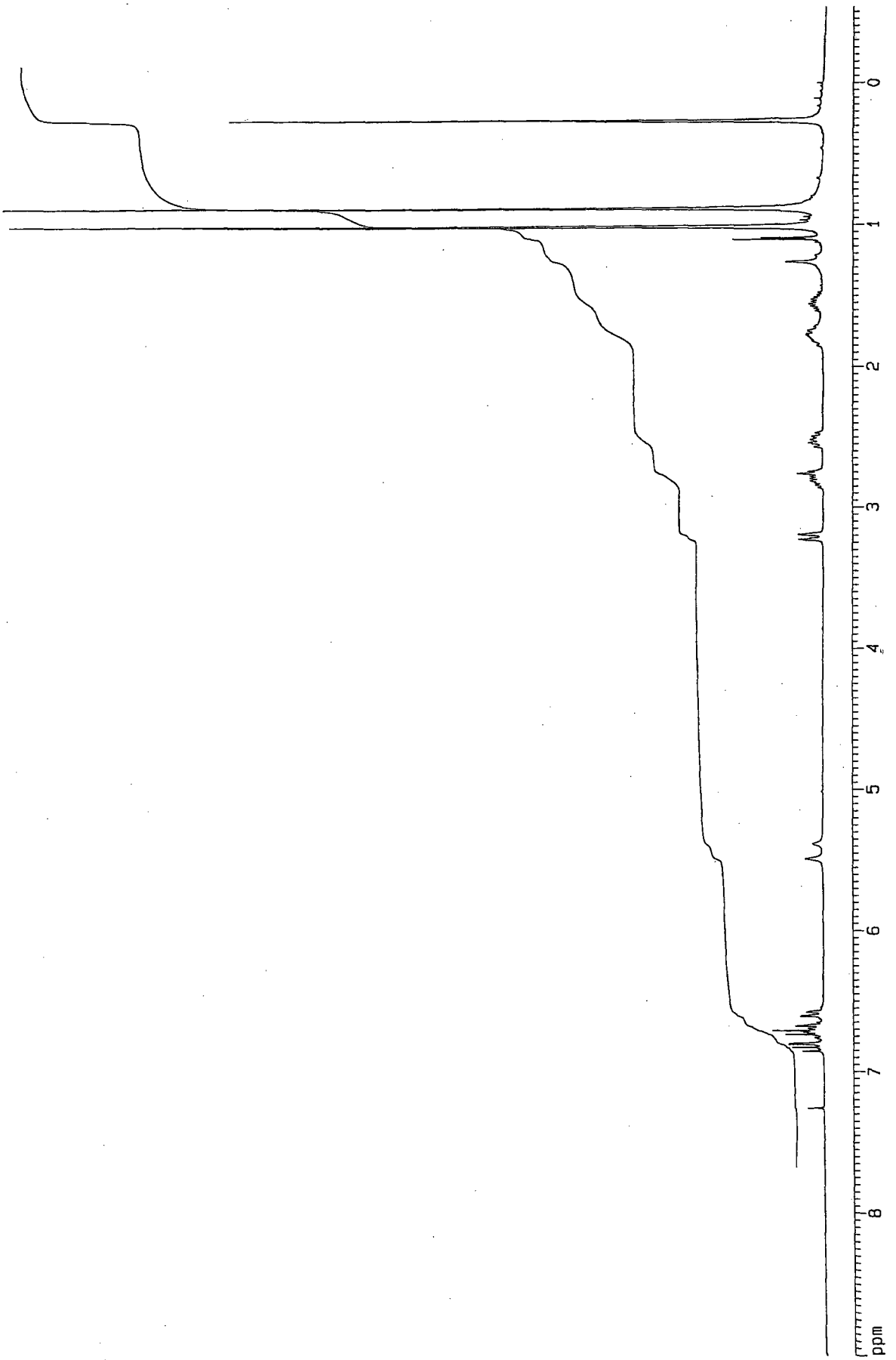
^{13}C-NMR Spectrum of
(±)-1-(3-(2,6-dichlorobenzyloxy)-4-hydroxy)-4,4-dimethyl-3-pentanol (**24d**)



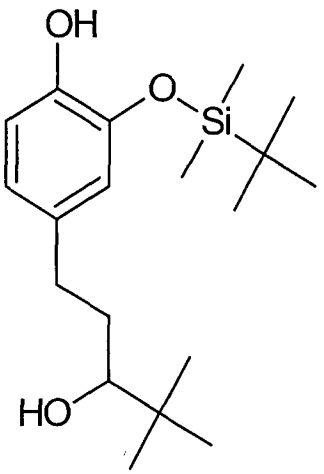

0
50
100
150
200
ppm

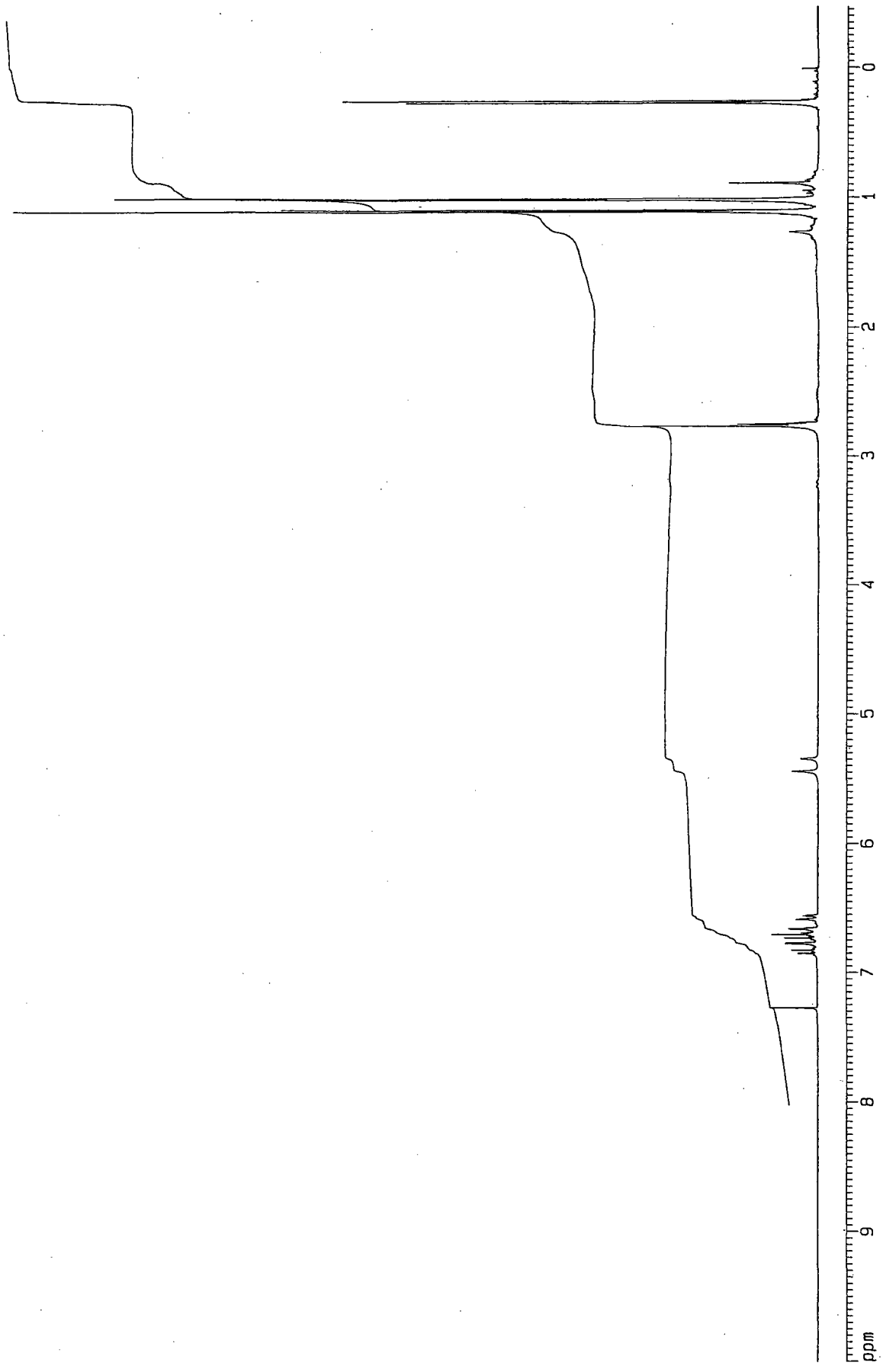
^{1}H-NMR Spectrum of Non-Chromatography Purified
(±)-1-(3-t-butyldimethylsilyloxy)-4-hydroxy)-4,4-dimethyl-3-pentanol (**24e**)



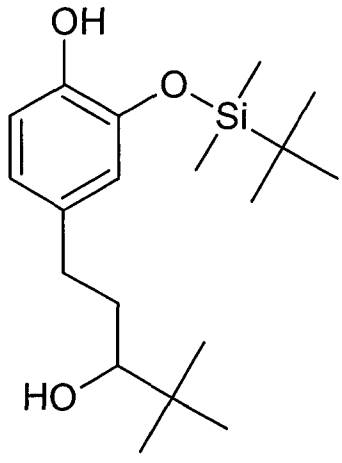

0
1
2
3
4
5
6
7
8
ppm

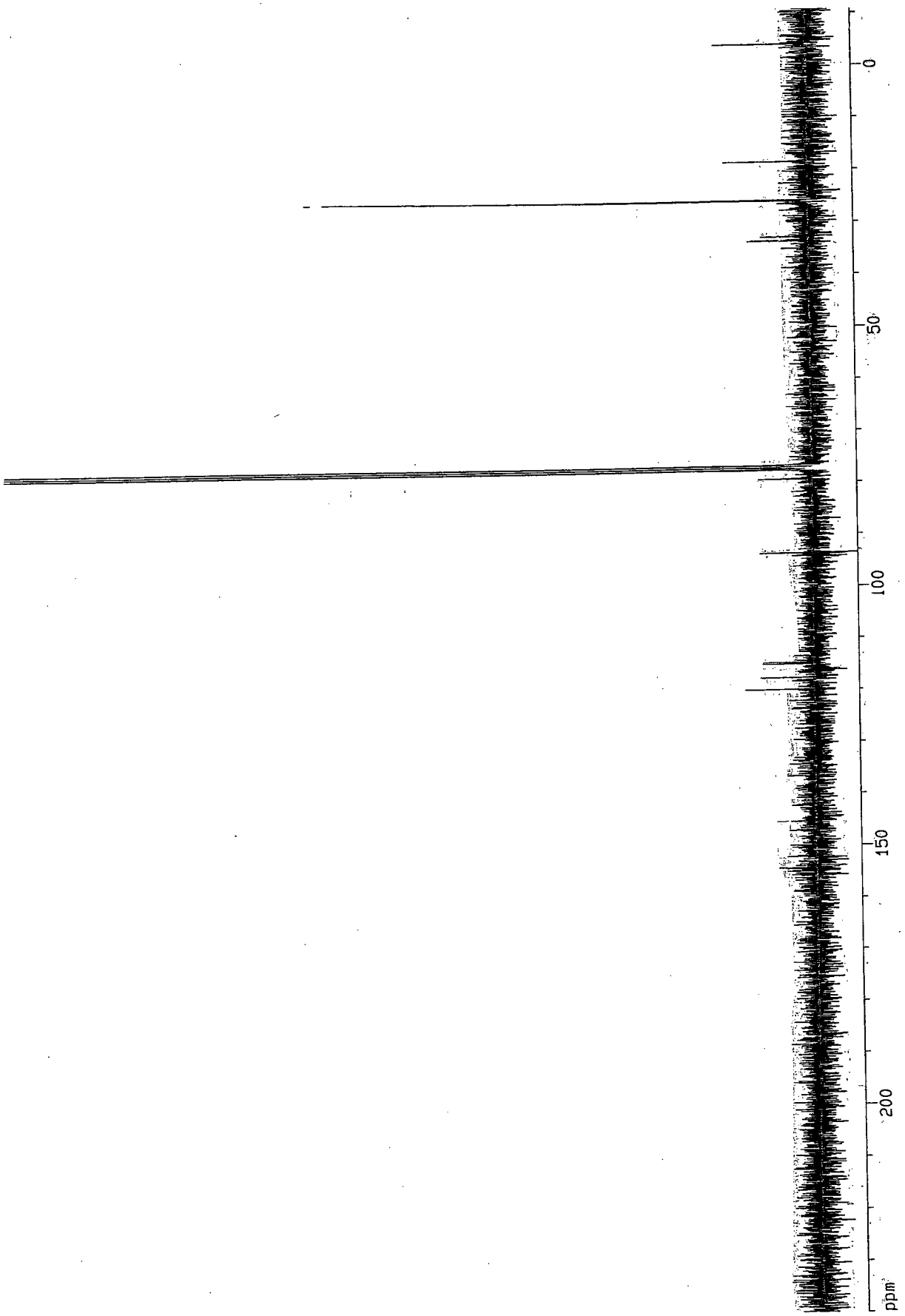
^{1}H-NMR Spectrum of Chromatography Purified
(±)-1-(3-t-butyldimethylsilyloxy)-4-hydroxy)-4,4-dimethyl-3-pentanol (**24e**)



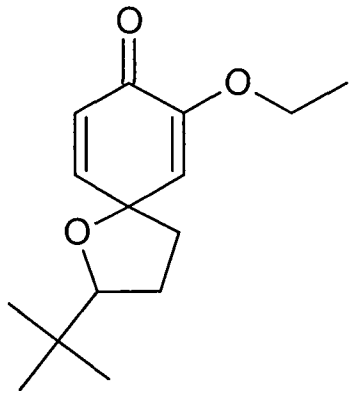

0
1
2
3
4
5
6
7
8
9
ppm

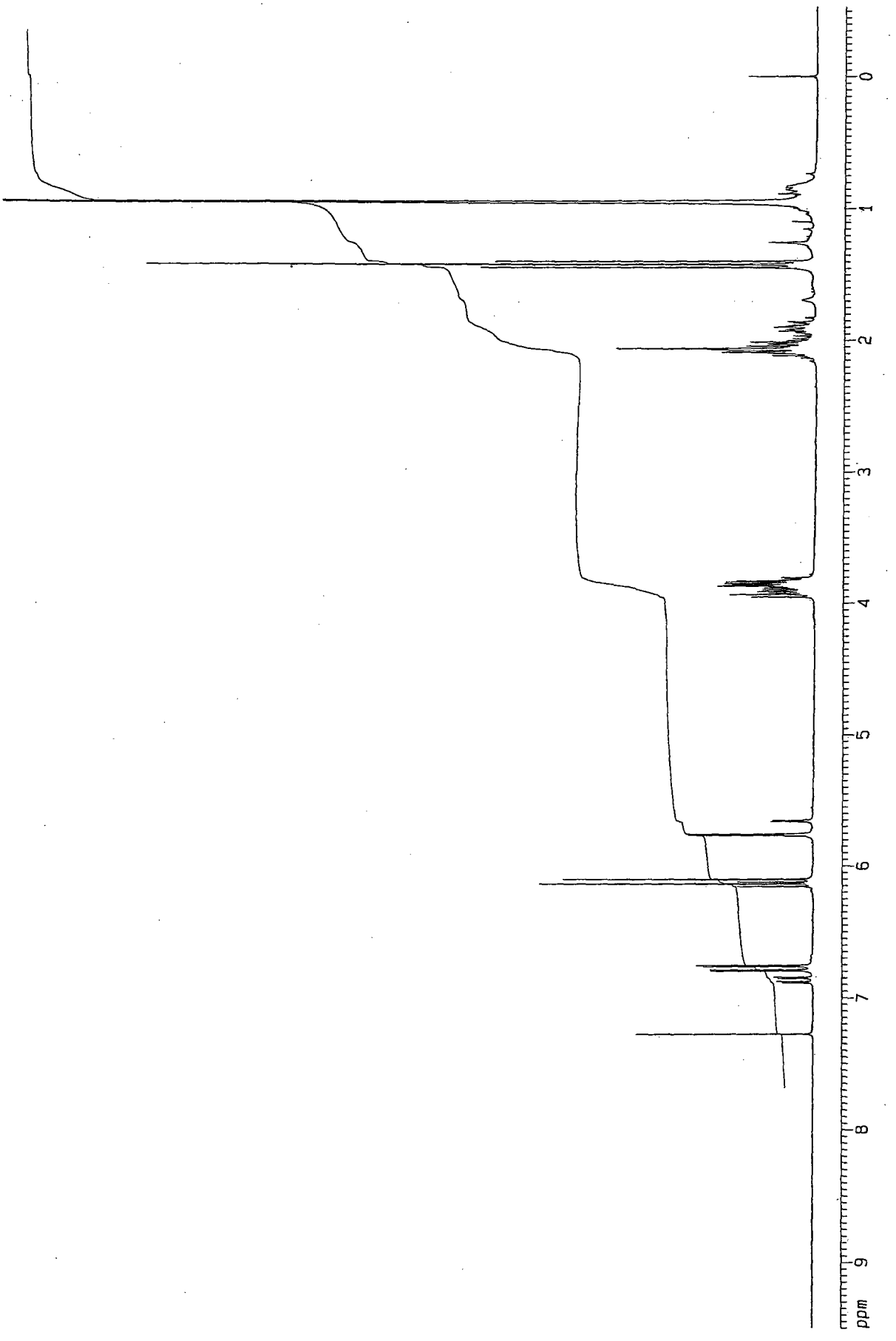
^{13}C-NMR Spectrum of
(±)-1-(3-t-butyldimethylsilyloxy)-4-hydroxy)-4,4-dimethyl-3-pentanol **(24e)**



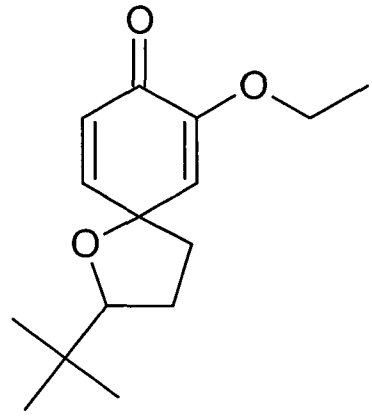

0
50
100
150
200
ppm

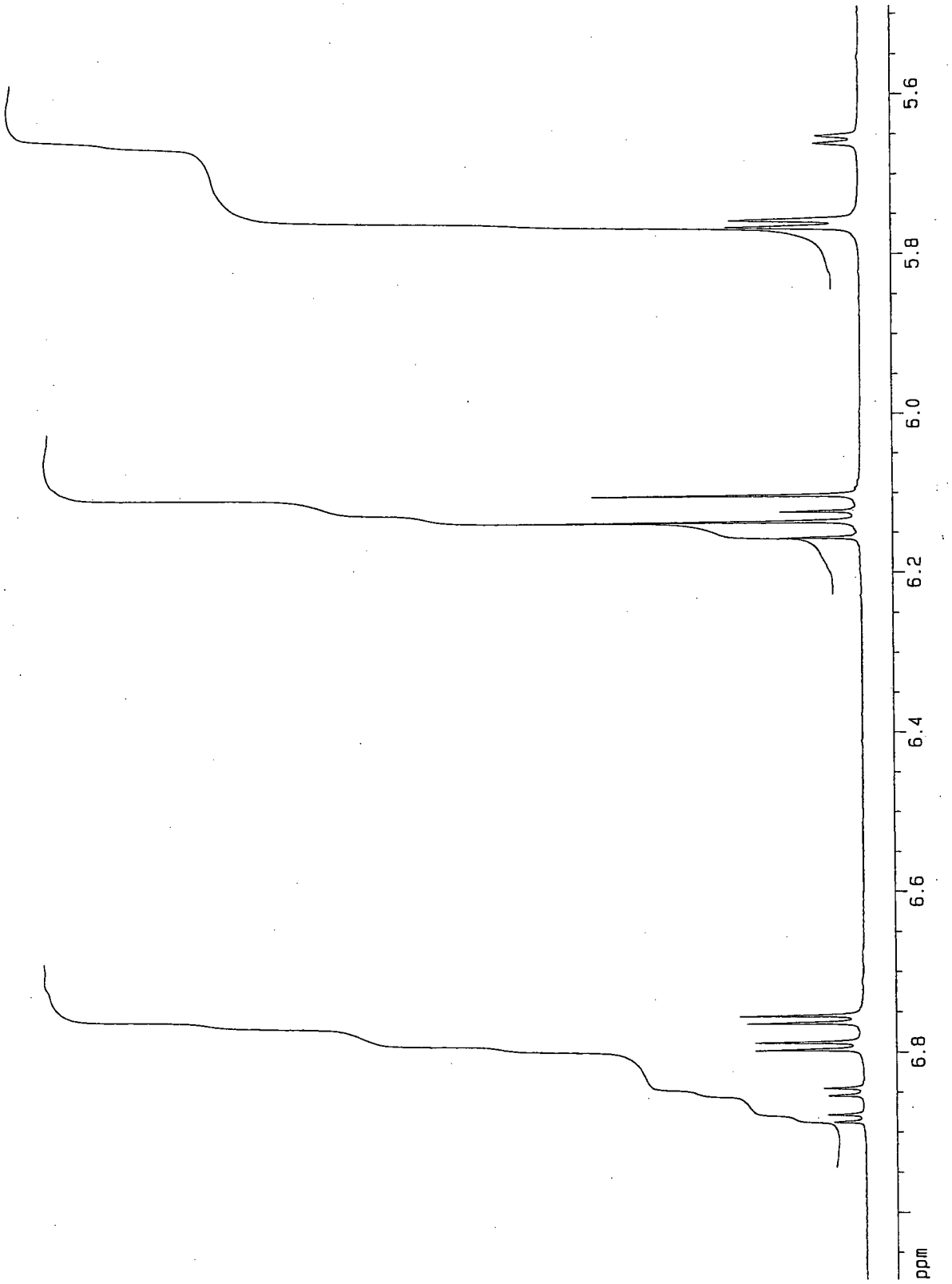
^{1}H-NMR Spectrum of
(±)-2-tert-Butyl-7-ethoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26a**)



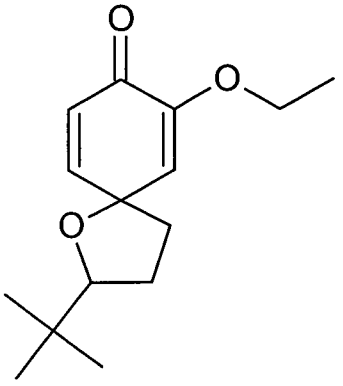

0
1
2
3
4
5
6
7
8
9
ppm

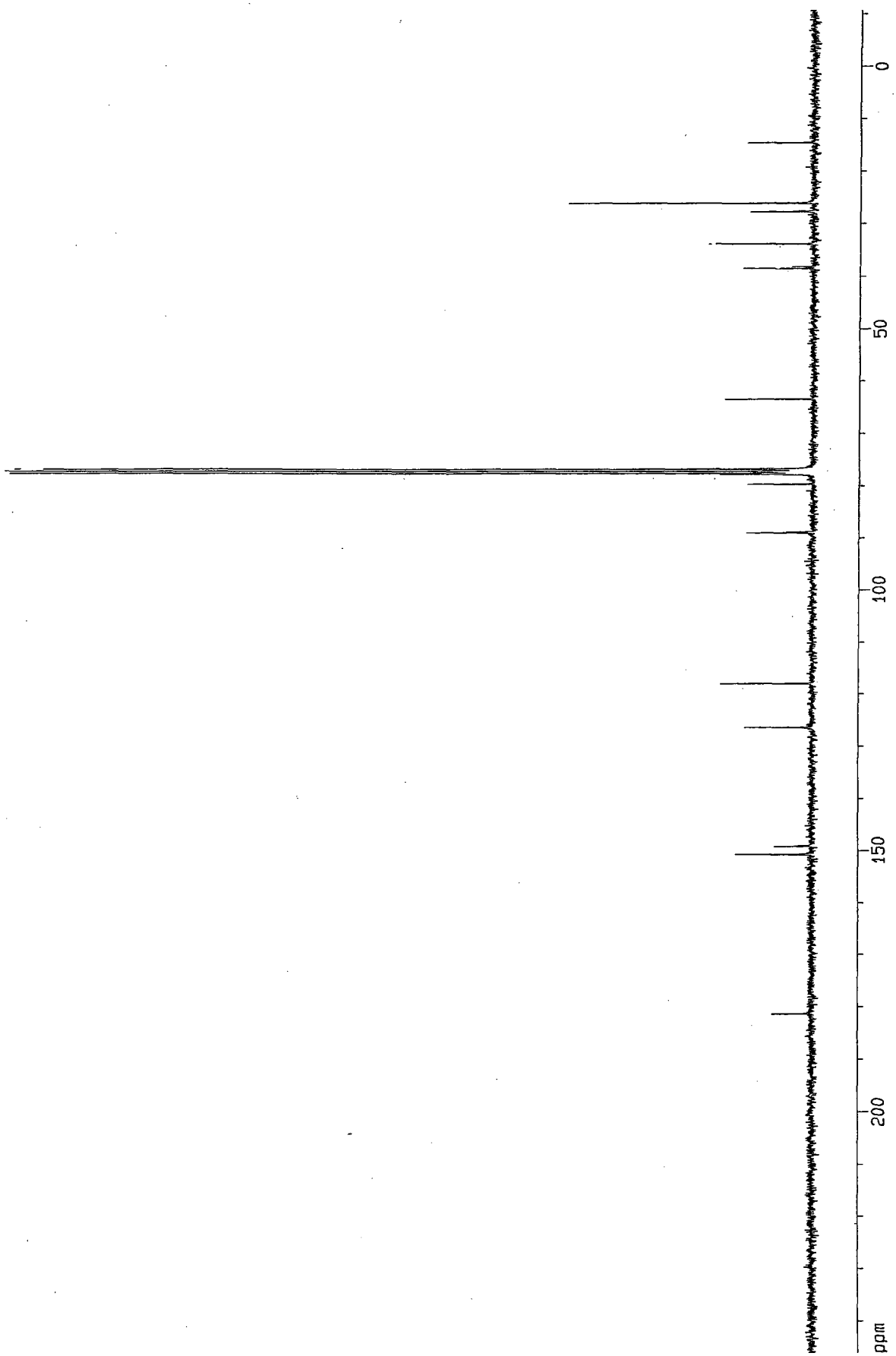
^{1}H-NMR Spectrum Expansion of
(±)-2-tert-Butyl-7-ethoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26a**)



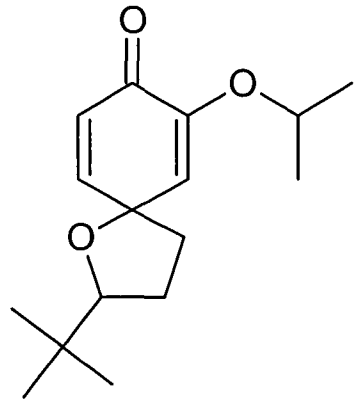

5.6
5.8
6.0
6.2
6.4
6.6
6.8
ppm

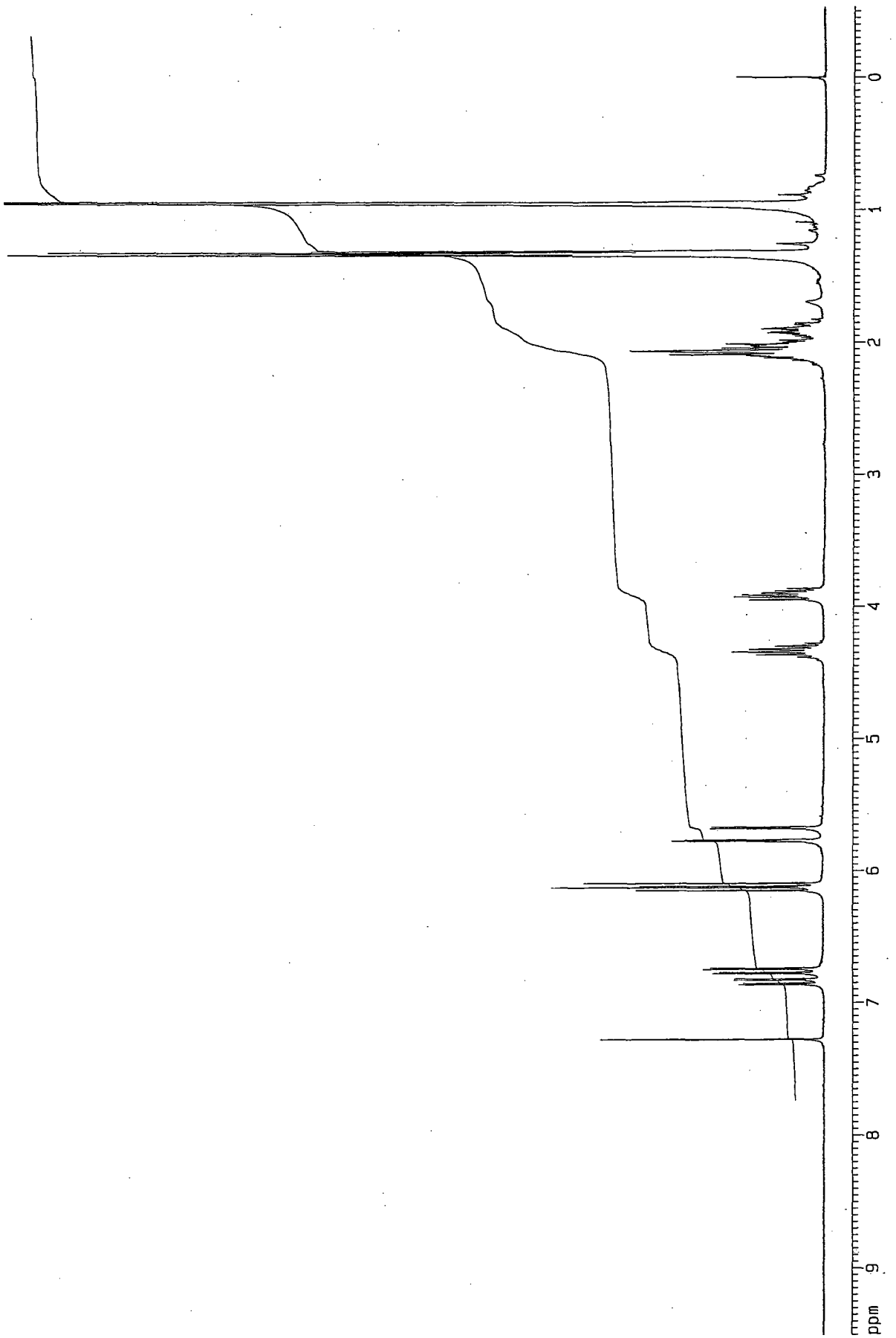
^{13}C-NMR Spectrum of
(±)-2-tert-Butyl-7-ethoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26a**)



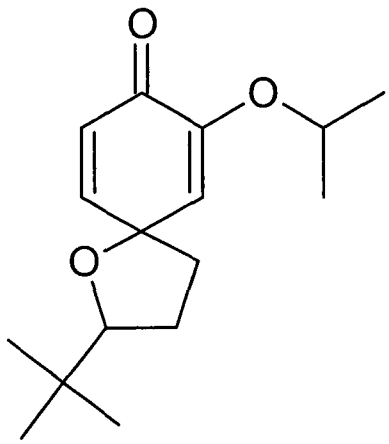

0
50
100
150
200
ppm

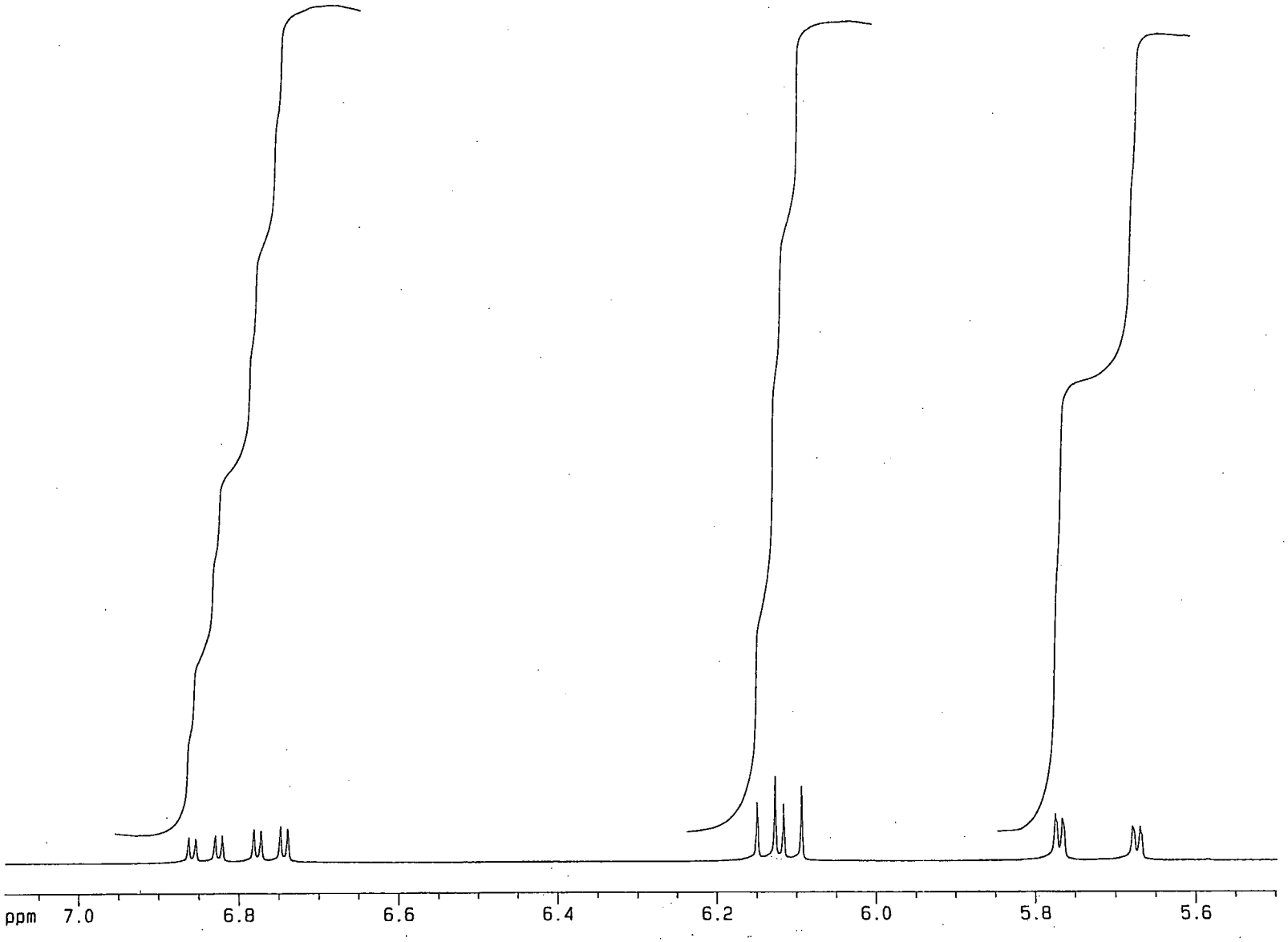
^{1}H-NMR Spectrum of
(±)-2-tert-Butyl-7-isopropoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26b**)



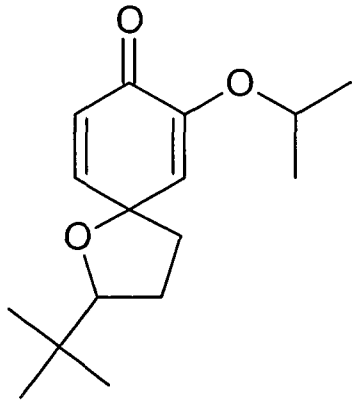

0
1
2
3
4
5
6
7
8
9
ppm

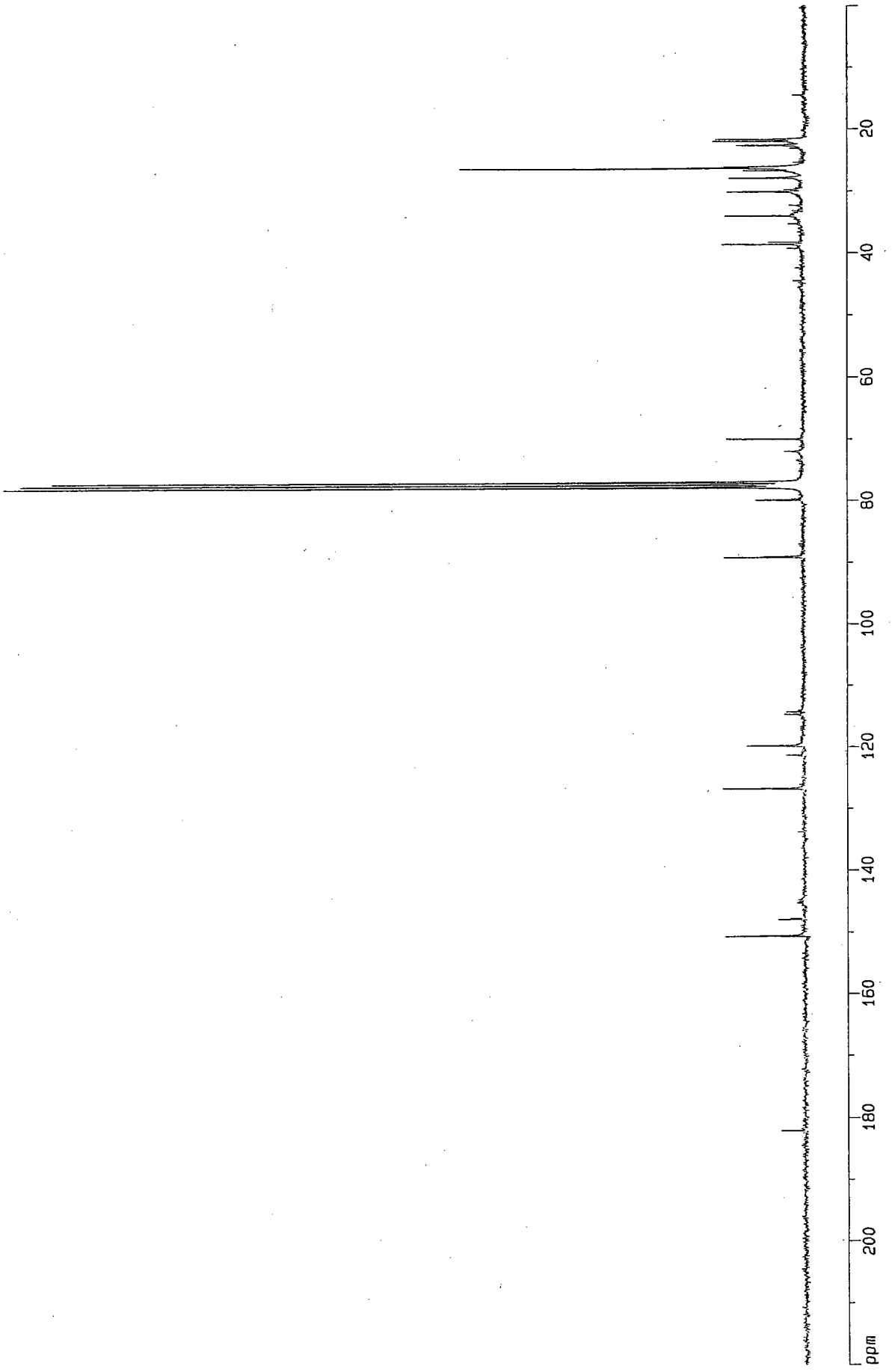
^{1}H-NMR Spectrum Expansion of
(±)-2-tert-Butyl-7-isopropoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26b**)



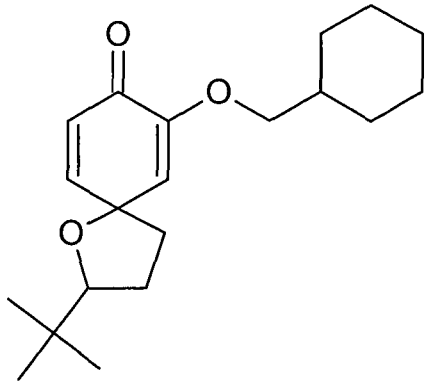

ppm 7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6

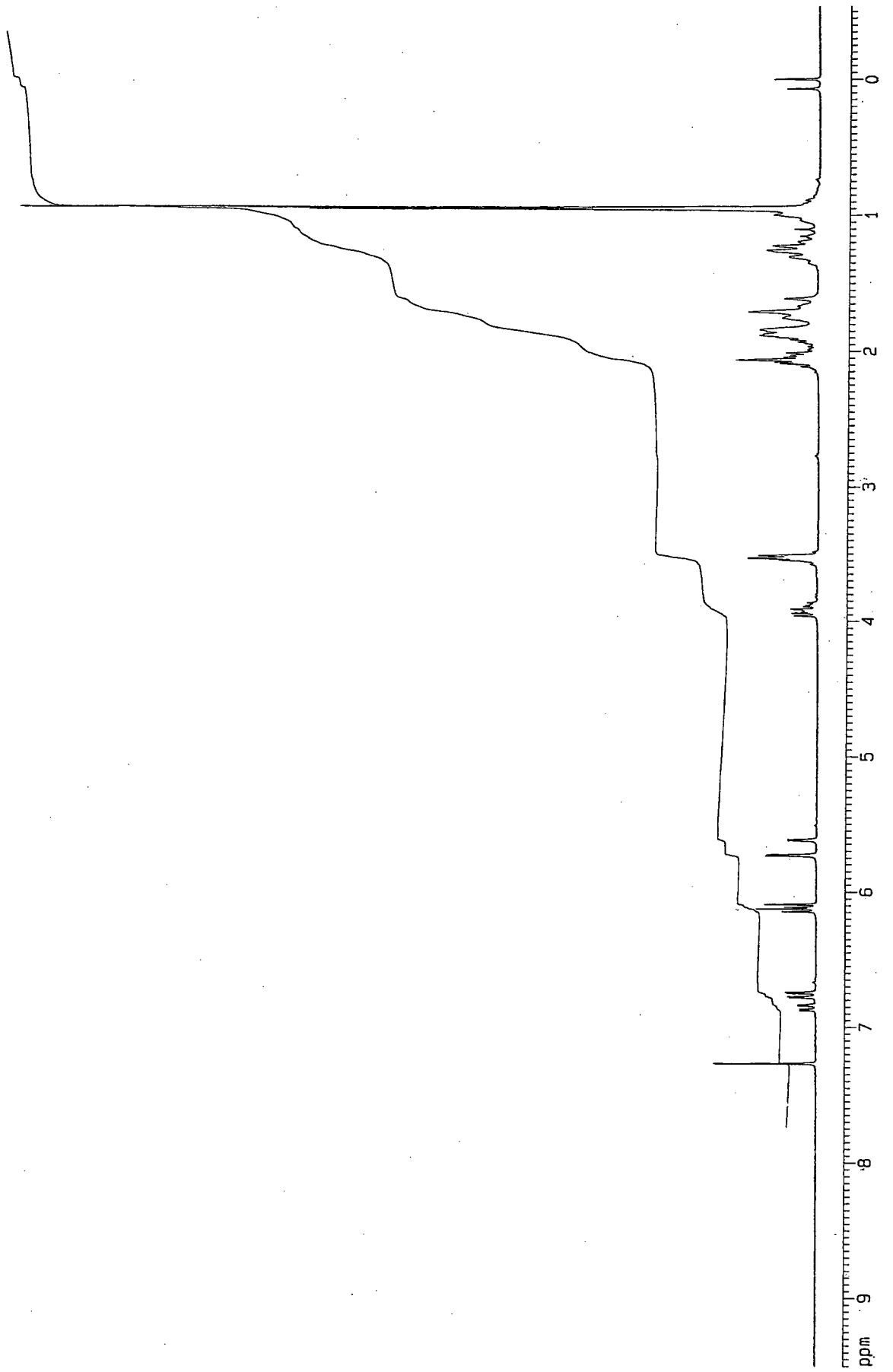
^{13}C-NMR Spectrum of
(±)-2-tert-Butyl-7-isopropoxy-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26b**)



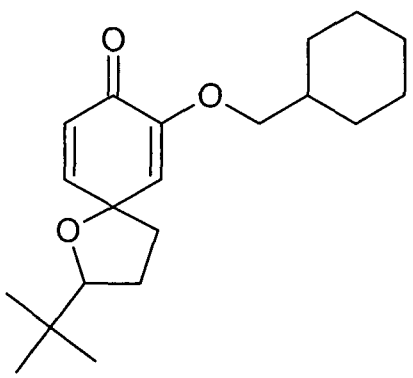

20
40
60
80
100
120
140
160
180
200
ppm

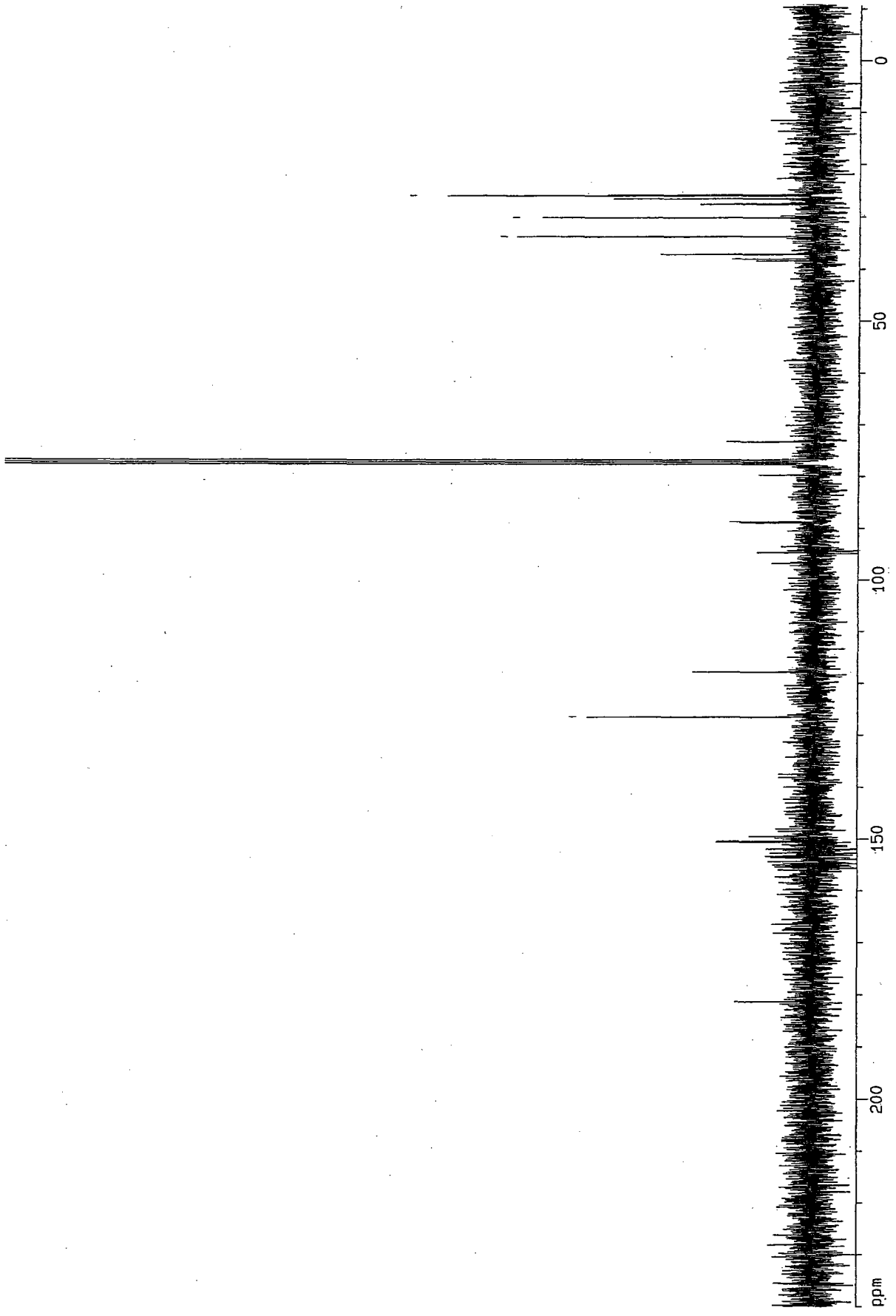
^{1}H-NMR Spectrum of
(±)-2-tert-Butyl-7-methylcyclohexyloxy-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26c**)



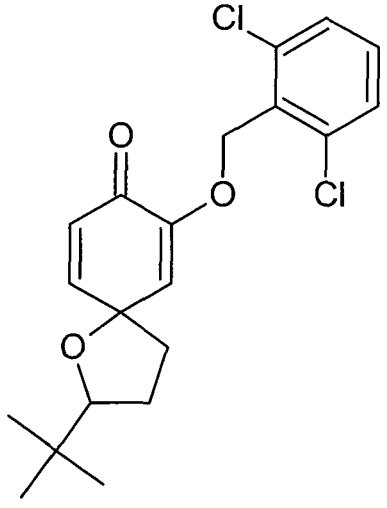

0
1
2
3
4
5
6
7
8
9
ppm

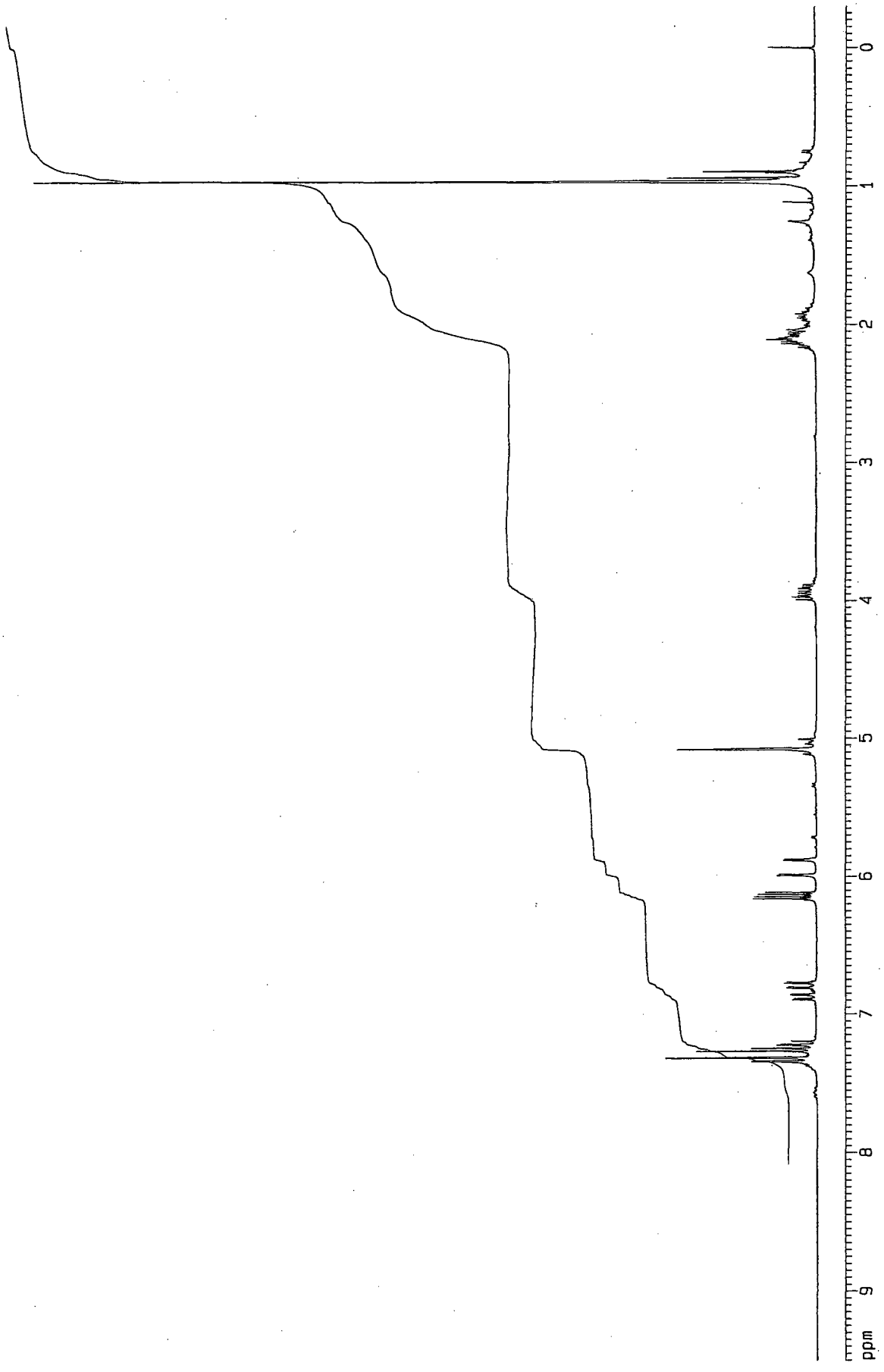
^{13}C-NMR Spectrum of
(±)-2-tert-Butyl-7-methylcyclohexyloxy-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26c**)



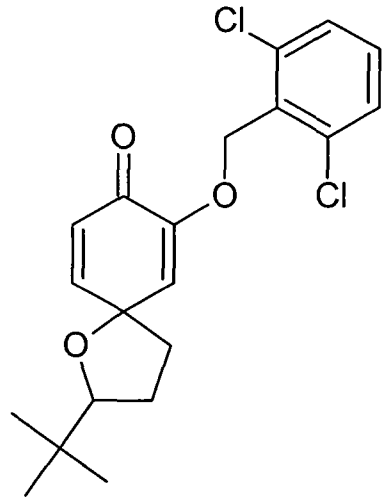

0
50
100
150
200
ppm

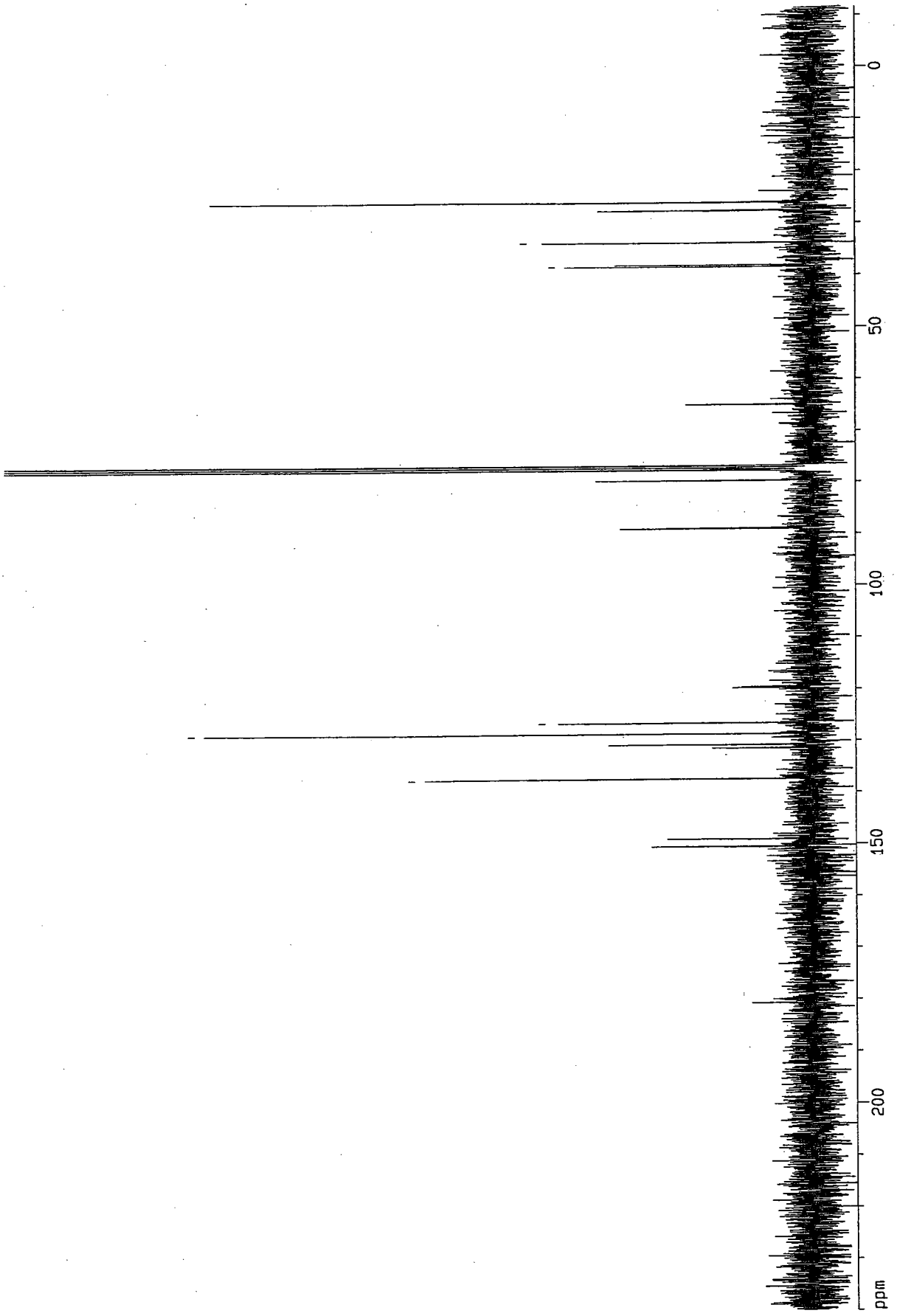
^{1}H-NMR Spectrum of
(±)-2-tert-Butyl-7-(2,6-dichlorobenzyloxy)-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26d**)



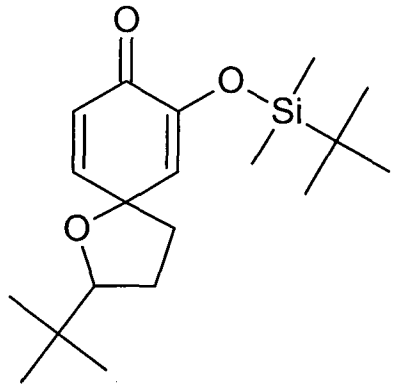

ppm
9
8
7
6
5
4
3
2
1
0

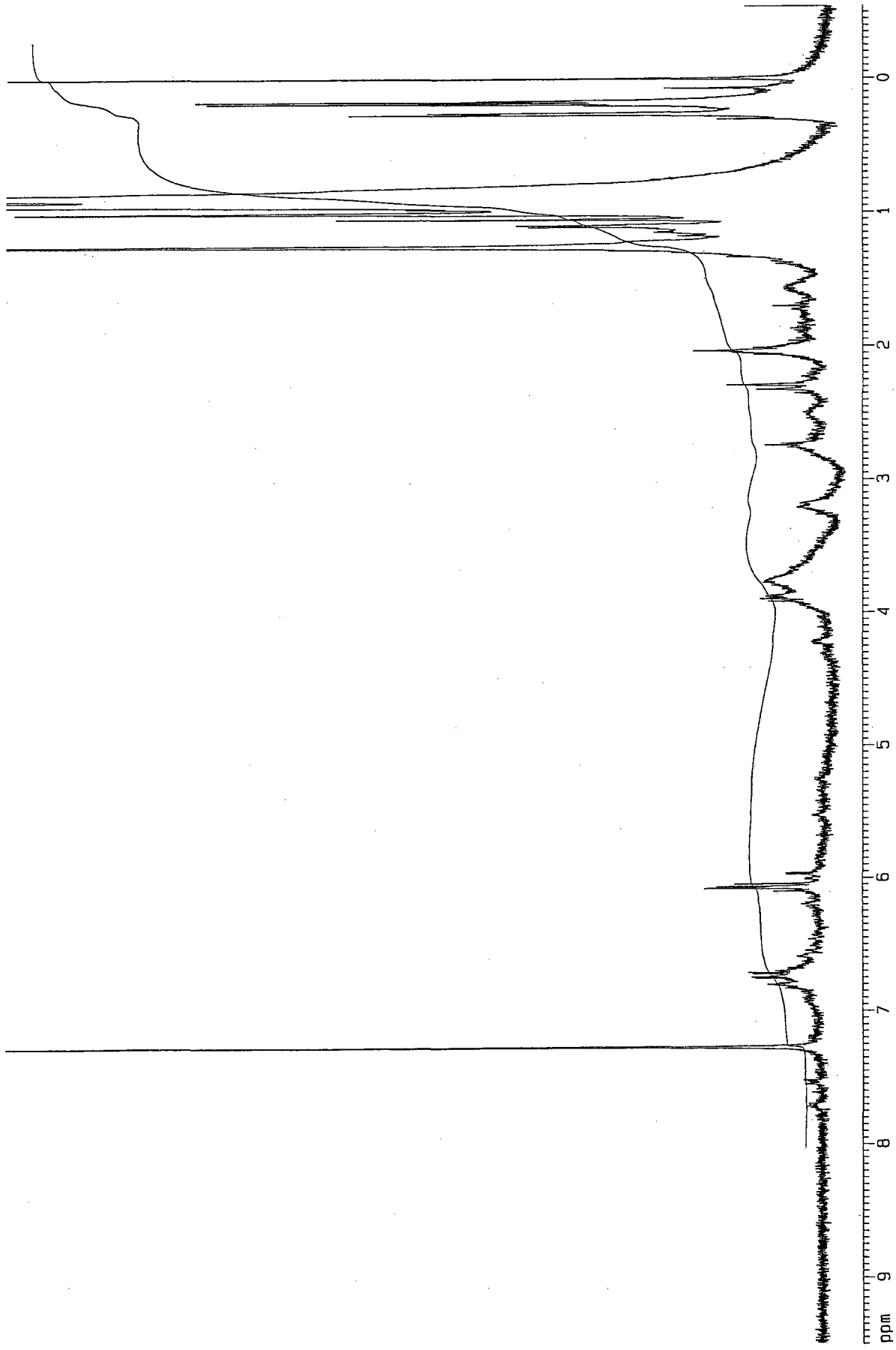
^{13}C-NMR Spectrum of
(±)-2-tert-Butyl-7-(2,6-dichlorobenzyloxy)-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26d**)




0
50
100
150
200
ppm

^{1}H-NMR Spectrum of
(±)-2-tert-Butyl-7-(t-butyldimethylsilyloxy)-1-oxaspiro[4,5]deca-6,9-diene-8-one (**25/26e**)




0
1
2
3
4
5
6
7
8
9
ppm

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